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January 10, 1974



See page 11

Page

RESEARCH ADVANCES:

Siamese Cats Found to be Model for Lipid Storage Diseases.....	1
Kanamycin Ointment Reduces Dental Plaque.....	4
New Theory on Blood Clotting Sparks Search for New Inhibitor.....	7

NEWS & PHOTO FEATURES:

Adult Chinook Salmon Used in Blood Research.....	11
Intensive Coronary Care Units Improve Heart Attack Survival.....	14
New "Ocuser" Provides Continuous Eye Medication.....	18

MEDICAL NEWS TIP:

Epilepsy Treatment.....	19
-------------------------	----

NEWS RELEASES ISSUED:

Cancer Virus, Clinical Center.....	20
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Research Advances

SIAMESE CATS FOUND TO BE MODEL
FOR LIPID STORAGE DISEASES

Investigations by a University of Alabama-Birmingham (UAB) scientist are providing important new revelations on the cause of inherited metabolic defects which cause progressive mental retardation. The studies give hope to parents who carry these genetic defects and to their afflicted children.

Henry Baker, D.V.M., an associate professor of Comparative Medicine at the UAB Medical Center, has found through studies with an unusual family of Siamese cats a disease which appears identical to an inherited brain disease of children known as juvenile GM₁ gangliosidosis. Like their human counterparts, kittens with this disease lack the activity of a single enzyme known as beta-galactosidase and, as a result, suffer a progressive deterioration of the nervous system. Having defined the basic metabolic defect, Dr. Baker and his associates are now undertaking studies to help find a treatment for these degenerative and eventually fatal diseases.

While there are several neurological disorders in this category, the best known of the group is Tay-Sachs disease which principally affects Ashkenazic Jewish children (those with Eastern Europe ancestry). In the cats

(more)

Studies by Dr. Henry Baker at the University of Alabama-Birmingham have shown the Siamese cat to be one of the best animal models yet for human enzyme deficiency diseases such as Tay-Sachs disease. (NIH Photo #1183)



NEWS & FEATURES From NIH

January 10, 1974

Lipid Storage Diseases (Cont'd)

and in man, the abnormal genes are carried by apparently normal individuals, and the disease is expressed in the offspring only when both parents carry the defect. Within the past two years it has become possible to detect carriers of Tay-Sachs disease by laboratory tests. As a result, Jewish communities in some large cities are being surveyed for this trait in an attempt to prevent the birth of diseased children.

By contrast, related types of disorders occur throughout the population, and the genetic defect is detected only after the birth of a retarded child.

Siamese kittens with GM₁ gangliosidosis appear normal at birth and successfully achieve all developmental milestones up to four months of age when head and hind limb tremors appear. Over the next four months, the tremors become more pronounced and the kittens develop a clumsy gait which progresses to generalized locomotor ataxia (difficulty in coordinating voluntary movements).

Spastic paralysis of all four limbs, accompanied by evidence of impaired vision, ensues by seven to eight months of age. At age one, they show exaggerated locomotor ataxia and recurring epileptic-like seizures.

The clinical hallmarks of juvenile GM₁ gangliosidosis (Type II) of children are essentially identical to those observed in the Siamese cats.

The UAB studies have pointed up the Siamese cat to be one of the best animal models of human enzyme deficiency diseases yet discovered. This discovery was significant enough for the NIH Division of Research Resources to give support in 1971 through their Animal Resources Branch to establish a breeding colony of these cats for biomedical research.

(more)

Lipid Storage Diseases (Cont'd)

It is not possible to estimate accurately the incidence of this genetic defect in the Siamese breed. However, its occurrence in cats from England, Japan, and elsewhere in the United States supports the possibility that this disease might be a significant inherited defect in the world's most popular breed of cats. As a veterinarian, Dr. Baker is particularly interested in these findings because his studies ultimately will benefit both man and animals.

Because at present physicians cannot successfully treat children afflicted with these ultimately fatal diseases, studies of possible methods of treatment are being emphasized by Dr. Baker and colleagues. For example, it is already possible to correct certain types of enzyme deficiencies of cells cultured in test tubes by administration of purified enzyme. It may be possible to replace or reactivate the defective enzyme. The investigators hope that administration of enzyme purified from healthy tissues can replace the function of the defective enzyme in a cat, and ultimately in a child.

Another possible method of treatment is transplantation of a healthy organ, such as a kidney, to a diseased child. Scientists have reasoned that the normal organ may provide a continuing source of functional enzyme for use by all tissues of the recipient child.

Others collaborating in this research include scientists at the University of California and the Johns Hopkins University. The work is currently supported under a grant from the National Institute of Neurological Diseases and Stroke. Dr. Baker will publish a report of his findings in the March 1974 issue of the *American Journal of Pathology*.

Research Advances

Studies Continued...

KANAMYCIN OINTMENT
REDUCES DENTAL PLAQUE

After a one-year study, National Institute of Dental Research grantees find that kanamycin ointment applied to the buccal surfaces of all teeth every five weeks (at least once a day for several days) can reduce the amount of dental plaque and inflammation of the gingiva in children unable to brush their teeth.

Additionally, the untreated areas in the mouth seem to benefit as much as the treated ones, according to Walter J. Loesche, D.M.D., Ph.D., of the University of Michigan's Dental Research Institute and Don Nafe, D.D.S., of the Plymouth State Home and Training School, Northville, Michigan.

The researchers studied a small group of 15 children with Down's Syndrome and treated the children at five-week intervals because previous tests showed that the drug was effective at least for this period. Most children were moderate to heavy plaque formers.

According to the scientists, the study children had less inflammation and produced much less plaque than when they were not treated. Only three children did not benefit as much from the treatment--two of them had very little plaque with or without kanamycin, and one formed a very large amount of plaque which rapidly hardened into calculus.

Before beginning the treatment, the investigators found that five weeks after a professional cleaning, the children's teeth and gingiva were in the same condition as before. They divided the group and rubbed the buccal or

(more)

Kanamycin (Cont'd)

labial surfaces of all teeth in each child in one section with a plain ointment and treated the other children similarly with the ointment mixed with five percent kanamycin. The tongue and cheek surfaces of the selected teeth were rubbed twice a day for five days at first. Thereafter, no brushing was done for five weeks when the children were again inspected, and the plaque from the treated teeth was removed and weighed. The researchers gradually decreased the applications until they were applying the drug just three times on successive evenings.

Although the ointments were coded, the investigators could easily tell which children received the antibiotic because they had less inflammation and plaque. For example, the heavy plaque-former developed about 65 percent less plaque with the drug, but still had calculus.

After 15 weeks, the investigators gave all the children kanamycin. At week 20, they found no visible difference between those who had received it all along and those who had just begun treatments. Reducing applications from ten to three made no visible difference either, suggesting that a maintenance dose could be employed once the plaque levels were under control.

After week 40, all treatments were stopped, and by week 52 plaque accumulations and inflammation scores had returned to pretreatment levels.

The scientists also tested the organisms in the children's mouths before and after the kanamycin treatments, and found no more were resistant to the antibiotic at the end of the year than at the beginning--about six percent. They believe that since no bacterial resistance to the antibiotic developed, and since a few treatments produced marked reduction of plaque

(more)

Kanamycin (Cont'd)

and inflammation over long intervals, it is logical to employ kanamycin or similar agents to reduce certain dental problems in institutionalized patients unable to help themselves--especially when there is not enough manpower to clean teeth properly.

The findings reported in the *Archives of Oral Biology*, September 1973, result from a continuation of shorter-term studies reported in 1971.

#

SIDS--The sudden infant death syndrome (SIDS) is the leading cause of death in infants after the first month of life, claiming the lives of three infants for every thousand live births, according to the National Institutes of Health.

GLAUCOMA--Glaucoma is an eye disease which strikes one out of every 200 people in the United States over age 40, according to the National Institutes of Health.

RETINAL DISEASES--Diseases of the retina, the light-sensitive tissue at the back of the eye that transmits visual information to the brain, account for more blindness and visual disability in the United States than any other cause, according to the National Institutes of Health.

Research Advances

NEW THEORY ON BLOOD CLOTTING
SPARKS SEARCH FOR NEW INHIBITOR

A blood specialist has suggested that clotting in diseased human arteries resembles clotting in lobster closely and this might explain why powerful anti-clotting agents are not always effective in heading off deadly blood clots, as in the case of heart attacks and strokes.

Koloman Laki, Ph.D., of the National Institute of Arthritis, Metabolism, and Digestive Diseases, recently described animal experiments showing how hardened and fat-laden arteries may cause blood to clot in the way it does in the lobster and other primitive species. With this ancient clotting process at work, anti-clotting agents such as heparin and coumarin would not necessarily keep a clot from forming and plugging up blood vessels. Dr. Laki suggests looking at primitive blood clotting systems for natural substances which may work to thwart the process.

According to Dr. Laki, the clotting process in man is a two-edged sword. Normally it works to prevent fatal loss of blood by plugging injured vessels. However, blood clots often form inside the vessel and shut off blood flow. Such clots in the coronary arteries nourishing the heart can lead to a heart attack; in a vessel leading to the brain, a stroke.

The clotting process in man is a very complicated affair involving a chain of blood substances operating in delicate sequence. According to the classical view of clotting, at the end of this long sequence of chemical events an active substance called thrombin is formed from a precursor chemical, prothrombin. The thrombin acts on the blood substance fibrinogen

(more)

Blood Clotting (Cont'd)

to change it into a thread-like substance, fibrin, which forms the actual clot.

Recently, Dr. Laki and his colleagues discovered that in the body, in addition to fibrin, a second enzyme is involved in fixing the fibrin clot. Where thrombin alone produces only a weak bond between fibrin molecules, this second agent, called transglutaminase, acts as a powerful glue, cementing these bonds and making them firm. The enzyme is found in the blood of man and other vertebrates in the form of an inactive precursor called Factor XIII.

"It is very important to realize that the transglutaminase generated from Factor XIII is a true clotting enzyme," Dr. Laki says. "In its absence, there is no hemostasis [the medical term for non-bleeding] and no proper wound healing. The clot formed by thrombin alone is a preliminary step, without the action of the second enzyme, the clot may not constitute any grave danger of thrombosis (dangerous, inside-the-vessel clotting)."

Dr. Laki believes that transglutaminase is a clotting enzyme which can be traced hundreds of millions of years down the evolutionary scale. Lobster blood, for example, has no thrombin. Rather, transglutaminase clots fibrinogen (the precursor of fibrin in man) directly.

Apparently what happened in the course of evolution, Dr. Laki explains, is that the thrombin system was added in vertebrates to the original transglutaminase system in order to put the clotting process under sharper control. Nature's main innovation here was to make transglutaminase act on fibrin and not on fibrinogen, as in the lobster. However, in man its action on fibrin

(more)

Blood Clotting (Cont'd)

is not absolute, Dr. Laki said. Human fibrinogen can be clotted directly by activated Factor XIII if present in high enough concentration.

This indicates that if too much transglutaminase comes into operation a patient may die from a fibrinogen clot even if he is being treated with coumarin or heparin, which interfere only with the thrombin manufacturing process.

Dr. Laki cites experimental evidence implicating diseased walls of arteries as regions where transglutaminase levels increase substantially. In his experiments, he has fed rabbits a high cholesterol diet for several weeks in order to produce atherosclerosis. Dr. Laki examined the animals' aortas and found the diseased portions (amounting to only about 10 percent of the entire aorta) containing on the average three times more transglutaminase than the remaining healthy 90 percent.

Dr. Laki sees these diseased vessel regions as "danger points," where transglutaminase levels may be high enough to directly clot any fibrinogen coming into contact with it.

Other researchers have evidence to bolster this idea, including indications that a mini-clot, usually seen as part of an advanced atherosclerotic deposit, is not really a web of fibrin but actually a network of fibrinogen threads.

Dr. Laki suggests additional research to test this notion of fibrinogen clotting in man, as well as a search for inhibitors which might prevent transglutaminase action. "We can expect nature to have invented specific inhibitors for transglutaminase just as it invented heparin for inhibiting

(more)

Blood Clotting (Cont'd)

thrombin. A study of clotting in primitive animals where this system is predominant is the most likely project to yield such an inhibitor."

Dr. Laki presented his findings at the 46th annual Scientific Sessions of the American Heart Association, November 7-11, 1973.

NOTE TO EDITORS: The following article, "Adult Chinook Salmon Used in Blood Research," discusses another aspect of research from Dr. Laki's Laboratory of Biophysical Chemistry.

#

GROWTH--One of the most crucial requisites for the growth and development process in children is adequate nutrition, according to the National Institutes of Health.

CANCER--The overall incidence of cancer in men is increasing, a trend particularly marked among blacks, while in women it is decreasing, according to the National Institutes of Health.

Photo Feature

ADULT CHINOOK SALMON
USED IN BLOOD RESEARCH

Jules A. Gladner, Ph.D., of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), recently visited the Spring Creek National Fish Hatchery to collect blood and pituitary glands from adult chinook salmon returning to spawn.

At the hatchery, which is across the Columbia River from Hood River, Oregon, he worked with John Halver, Ph.D., of the Western Fish Nutrition Laboratory, Fish and Wildlife Service, Department of Interior.

Dr. Gladner and his associate Ms. Patricia A. Murtaugh have found that the chinook salmon has two blood coagulating systems--one similar to that found in humans and another, more simple, resembling the system in lower animals. They believe this to be the first time both systems have been found in a vertebrate.

Another finding, according to the scientists, is that salmon plasmin (an enzyme found in the blood plasma) can remain active at temperatures of minus 20 degrees centigrade--below the

(more)

The male king salmon are still alive when they are netted from the Columbia River and placed on a fish rack. A scientist carefully removes the tail section and collects a small quantity of blood from the male only for coagulation studies. (NIH Photo #1184)



Salmon (Cont'd)

range where human plasma remains active. If the factor can be isolated from the salmon, it may have a practical application in human medicine for dissolving blood clots.



In a joint project with Peter G. Condliffe, Ph.D., of NIAMDD, Dr. Gladner is studying the hormones of the salmon and lamprey pituitary glands, the master gland of the body. The pituitary gland is removed from the male and female salmon. Here, the scientist uses an electric drill equipped with a core bit to precisely remove a two inch plug of skin, tissue, and bone from the fish's head and spine. (NIH Photo #1185)

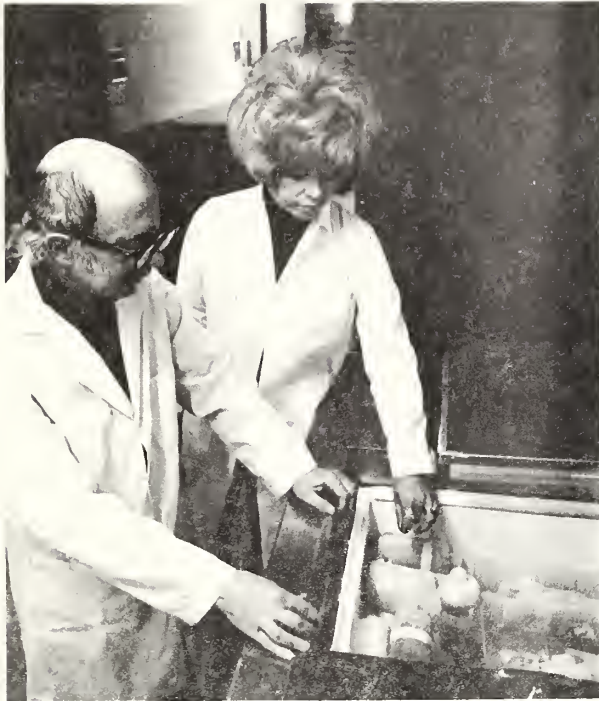
The plug then goes to a research biologist who removes the pituitary from the bone cave using a long, pick-like instrument to separate the gland from the other tissues. Pituitaries from the salmon, as well as those collected from lamprey eels and cattle, will be used in molecular biological studies of hormones produced by the gland. (NIH Photo #1186)

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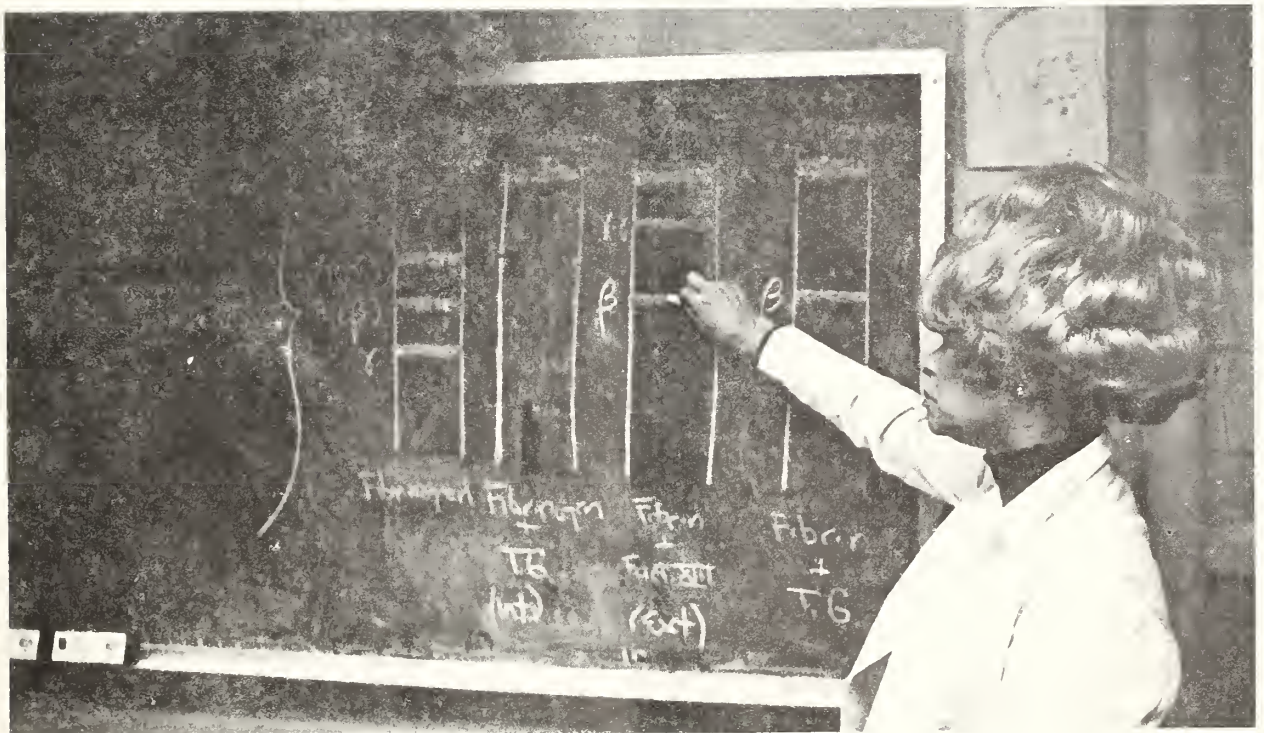


January 10, 1974

Salmon (Cont'd)



The blood plasma and pituitary glands of the male king salmon are packed in dry ice and shipped to Dr. Gladner's lab in Bethesda. The blood is drawn and plasma frozen during a two-week period. Here, Dr. Gladner and Patricia A. Murtaugh check the frozen blood plasma collected during a recent visit to Washington State. (NIH Photo #1187)



Ms. Murtaugh and Dr. Gladner use the salmon blood plasma in studies of enzyme action involved in blood clotting. Ms. Murtaugh displays some of their findings concerning the extrinsic and intrinsic systems of cross linking--the final step in blood coagulation in the king salmon.

(NIH Photo #1188)

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News-Feature

INTENSIVE CORONARY CARE UNITS
IMPROVE HEART ATTACK SURVIVAL

The advent of the intensive coronary care unit--combining close medical and nursing surveillance of heart attack patients with the advanced techniques for the prevention and control of heart-rhythm disturbances and other complications--has substantially improved survival rates among hospitalized heart-attack victims. Many people pioneered in the development of the instrumentation, concepts of patient care, and methodology that have made possible these advances in emergency coronary care and the saving of countless thousands of lives.

In 1947, Claude S. Beck, M.D., and co-workers from Western Reserve University, Cleveland, achieved the first successful termination of ventricular fibrillation and cardiac arrest in man. The technique involved emergency exposure of the heart via a chest incision, manual squeezing of the heart rhythmically to sustain an effective output, and the restoration of the heart-beat with AC shocks via insulated paddles applied directly to the heart muscle. The technique was widely and successfully applied to patients experiencing ventricular fibrillation in the operating or recovery room, but had little application elsewhere.

This heroic approach appeared excessively traumatic and complicated to Paul M. Zoll, M.D., of Beth Israel Hospital and Harvard Medical School. He found abundant evidence that heart muscle responded to small electrical shocks when these were delivered directly to it, and therefore reasoned that larger shocks, administered through the intact chest wall might similarly stimulate the heart despite attenuation by the resistance offered by intervening

(more)

Coronary Care Units (Cont'd)

tissues.

In 1952, AC stimulation via electrodes placed on either side of the intact chest was used for the first time against ventricular standstill in man. It quickly became established as an effective emergency procedure. In 1954, Dr. Zoll and co-workers also demonstrated that external AC countershock was effective against a number of other cardiac arrhythmias.

Bernard Lown, M.D., of the Harvard School of Public Health and Peter Bent Brigham Hospital, Boston, introduced direct current shock for the reversion of cardiac arrhythmias in 1962. By this time, AC countershock had become the standard electric treatment for serious heart rhythm disturbances, but had shown a tendency to trigger dangerous arrhythmias as well. Dr. Lown had long suspected that there might be advantages in some application of direct current instead.

The result of several years of such experimentation by Lown to find the optimal combination of energy, waveform, and timing was the concept of "cardioversion." The usefulness of cardioversion now ranges from the correction of many relatively minor and chronic arrhythmias to cardiac resuscitation in the gravest emergencies of acute coronary care.

Dr. Lown also helped to revolutionize the strategy of care for patients with acute heart attacks. With the view that "coronary death is not unannounced" in such patients, he has shown that the early detection and aggressive treatment of seemingly minor arrhythmias often obviate the need for heroic resuscitation procedures.

In 1960, Hughes W. Day, M.D., and colleagues at Bethany Hospital, Kansas City, Kansas, initiated a cardiac resuscitation program for the emergency

(more)

Coronary Care Units (Cont.'d)

treatment of cardiac arrest or other conditions posing an immediate threat to the patient's life. Called "Code Blue Emergency" because the patients were usually cyanotic, the program employed mobile crash carts containing defibrillators, pacemakers, emergency drugs, and other necessities for cardiopulmonary resuscitation. The "Code Blue Emergency" Program was the forerunner of the Intensive Coronary Care Unit.

However, early results proved disappointing. All too often cardiac arrests went undetected for vital minutes or were detected by nursing personnel inadequately trained in resuscitation procedures to sustain the patient until the crash cart could reach the scene. Dr. Day recognized the need for a special area where cardiac cases could receive the closest supervision, more adequate care could be given, impending serious complications could be prevented, and emergency situations could be detected promptly by nurses highly trained to respond quickly and effectively while other help was being summoned.

The first such unit, utilizing continuous monitoring of the electrocardiogram and an audible and visual alarm system to alert personnel at the nursing station of a present or impending emergency, demonstrated that such units could substantially reduce mortality from arrhythmias developing in the wake of acute heart attacks. Since 1964, such units have been established in ever-increasing numbers in hospitals large enough to make such units feasible.

Sudden death due to cardiac arrest can occur anywhere. For this reason, one of the most significant advances in emergency medical care was the development of a simple procedure that could be applied by anyone, anywhere to maintain the flow of blood in cardiac arrest victims. This procedure, known as closed-

(more)

Coronary Care Units (Cont'd)

chest (or external) cardiac massage, was developed in 1960 by W.B. Kouwenhoven, M.D., and James R. Jude, M.D., at Johns Hopkins University.

Closed-chest cardiac massage requires only the rhythmic application of pressure to the breastbone with the hands. This compression of the heart between the breastbone and the spinal column expels blood into the arterial circulation and, combined with mouth-to-mouth resuscitation, can maintain life for minutes or hours until definitive therapy becomes available.

Since its introduction 13 years ago, the use of closed-chest cardiac massage by firemen, rescue workers, and people in all walks of life has saved thousands of their fellow Americans from premature death due to cardiac arrest.

#

POPULATION--The U.S. population has increased 50 percent in the past 30 years and is expected to increase another 50 percent before the year 2000. The impact of population growth cannot be assessed without considering its effects on the health of children, families, and society as a whole, according to the National Institutes of Health.

Photo Feature

NEW "OCUSERT" PROVIDES
CONTINUOUS EYE MEDICATION

The Ocusert, a miniature dispenser inserted into the eye under the lower lid, is an extremely thin plastic wafer which allows a constant release of the correct dosage of medication.

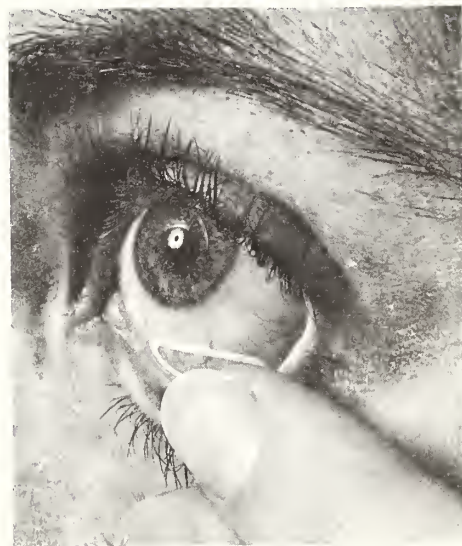
The device, developed by ALZA Corporation a California pharmaceutical firm, is undergoing testing in studies supported by the National Eye Institute.

The Ocusert insures around-the-clock delivery of medication, which particularly facilitates nighttime medication. Treatment is also easier and more convenient for the patient.

Because the Ocusert provides medication continuously and in the proper dosage, a smaller amount is needed to achieve the same therapeutic effect than in conventional drug therapy. In some cases



The Ocusert, as small as a teardrop, can provide a full week's supply of medication. (NIH Photo #1190)



The tiny Ocusert is positioned under the patient's lower eyelid. (NIH Photo #1189)

this might also lessen the risk of side effects from certain drugs.

This form of delivery may be beneficial for treating a wide variety of visual disorders including glaucoma, bacterial and fungus infections, and herpes simplex virus infection of the eye.

Medical News Tip

EPILEPSY TREATMENT--Gas-Liquid-Chromatography (GLC), a long-used method for measuring minute quantities of chemicals in solutions, has been used as a valid test to measure the levels of anticonvulsants in blood samples from epilepsy patients. This has greatly facilitated the treatment of patients with this disease.

Now applied to other standard and experimental drugs, GLC is helping neurologists and general practitioners to determine whether or not effective, non-toxic blood levels are being maintained, and to tell whether patients are taking their medicines as prescribed.

It is also valuable to researchers studying the effectiveness of old and new drugs.

For additional information about the use of GLC in epilepsy research, contact:

Information Office
National Institute of Neurological Diseases and Stroke
Bldg. 31, Room 8A-03
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News Releases Issued

CANCER VIRUS--American and Soviet cancer scientists have reported that a virus found by Soviet scientists in laboratory-grown human cells may belong to a new class of viruses with many of the known characteristics of animal cancer viruses. Scientists have not yet proven that these viruses have cancer-causing activity, although they possess certain characteristics of known cancer viruses. The cells were obtained by National Cancer Institute scientists from their Soviet colleagues as part of a joint collaborative program in cancer research.

CLINICAL CENTER--Robert S. Gordon, Jr., M.D., has been named associate director for Clinical Care of NIH and director of the Clinical Center. Dr. Gordon has been with NIH since 1951, serving first with the National Heart and Lung Institute and since 1964 as clinical director of the National Institute of Arthritis, Metabolism, and Digestive Diseases. He will be policy advisor for all clinical research conducted and supported by NIH as well as director of the Clinical Center.

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NEWS & FEATURES From NIH

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January 25, 1974



See page 9

RESEARCH ADVANCES:

	Page
Survey Examines Estrogen Use in Post Menopausal Women.....	1
Racial Differences in Tooth Decay Found in Hawaiian School Children.....	4
Study Compares Parents with Clefts and Siblings.....	7

NEWS & PHOTO FEATURES:

NCI Studies Particles of Cigarette Smoke.....	9
Usher's Syndrome Brings Deafness, Loss of Vision.....	11
Connecticut Scientists Conduct Nuclear Molecule Studies.....	15

MEDICAL NEWS TIP:

Fertility Studies.....	17
------------------------	----

CAPSULES:

Research Illustrated.....	18
---------------------------	----

NEW PUBLICATION:

<i>Do We Care About Research Animals?</i>	19
---	----

NEWS RELEASES ISSUED:

Smoking & Health.....	20
-----------------------	----

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Research Advances

Risk of Diseases...

SURVEY EXAMINES ESTROGEN USE
IN POST MENOPAUSAL WOMEN

A survey of post menopausal women in Boston has found the risk of gallbladder disease in estrogen users to be 2.5 times that of a control group. The survey findings show no significant associations between use of estrogens and venous thromboembolism, newly-diagnosed breast cancer, or benign breast tumors.

These findings from the Boston Collaborative Drug Surveillance Program (BCDSP) correspond to a previous report from the Program indicating that women using the Pill appear to be twice as likely to have gallbladder disease as non-users of similar age. (See *NEWS & FEATURES From NIH*, August 25, 1973.)

Investigating this problem under a research contract from the National Institute of General Medical Sciences, BCDSP investigators designed the present study to investigate the effects of estrogen compounds used in the treatment of post menopausal symptoms. Concern about the possible harmful effects of such use has come from at least three sources:

First, the estrogenic compounds of oral contraceptives are thought to be associated with venous thromboembolism and it is possible that a similar relationship holds for estrogen used after menopause.

Second, some breast cancers may be estrogen-dependent and such dependence may be a function of age. Thus, the findings that breast cancer appears to be unrelated to oral contraceptive use in younger women may not rule out the possibility of a connection between estrogens and these diseases in older women.

(more)

Estrogen (Cont'd)

Third, the recent identification of a relationship between use of oral contraceptives and gallbladder disease raises the question of whether a similar association exists for estrogen use after menopause.

The patient population in the present study was the same one used in the previous survey (reported in *Lancet*, June 23, 1973): nurses interviewed patients admitted to 24 hospitals in the greater Boston area between January and November 1972. Post menopausal women, 45 to 69 years of age were considered for this investigation.

In the overall series of 926 cases and controls, the BCDSF investigators found 98 women who used estrogen-containing compounds. (Of these, 85 used conjugated estrogen tablets. The remaining 13 patients used stilbestrol, ethinylestradiol, or an unspecified estrogen-containing drug.) As expected, the rate of estrogen use dropped sharply with age.

In the examination of estrogen use and gallbladder disease, the findings show that the risk of disease appears to be higher in post menopausal women who use estrogens than in those who do not. In contrast to users of oral contraceptives, no evidence of a relationship with duration of use could be found in post menopausal estrogen users.

In the area of venous thromboembolism, 14 percent of the cases used estrogens. The investigators find surprising the failure to identify a strong association between estrogen use and idiopathic venous thromboembolism since this is the strongest association that has been reported in younger women using the Pill. They attribute this to the lower doses given post menopausal women and conclude that the general belief that the risk of venous thromboembolism increases with age is probably a function of a higher prevalence of predisposing diseases.

(more)

Estrogen (Cont'd)

For breast tumors, the rate of estrogen use was 9 percent for breast cancer and 8 percent for benign breast tumors. The investigators found no evidence of association, either positive or negative, between estrogen and breast tumors, even when the group was divided into fibrocystic disease, fibroadenoma, and other tumors.

The BCDSF scientists find the results for breast cancer and tumors to be "reassuring." The data suggest to them that if any causal connection exists between estrogens and these diseases, they are unlikely to be strong. It is particularly encouraging to them that there is no suggestion of a higher risk even in long-term users. These results are in accord with those reported in relation to oral contraceptive use.

#

CHROMOSOMES--Errors in the structure and number of chromosomes are a leading cause of serious developmental disorders and mental retardation. It is estimated that at least one child in every 200 live births is so affected, and that the incidence of lethal chromosome abnormalities is 40 times greater in unborn infants, according to the National Institutes of Health.

Research Advances

RACIAL DIFFERENCES IN TOOTH DECAY
FOUND IN HAWAIIAN SCHOOL CHILDREN

A National Institute of Dental Research-supported study of Hawaiian school children has uncovered racial differences in tooth decay. This epidemiological study of the relationship between the frequency of eating various foods and the rate of tooth decay in adolescents showed that the differences persisted even after allowing for dietary variations.

Frequent consumption of candy and gum was the combination most conducive to decay. Hawaiians were the most susceptible to decay, Japanese next, Caucasians least.

Caries activity depends on interactions between certain bacteria in the mouth, the availability of carbohydrates in the diet for them to ferment, and the susceptibility or resistance of the individual's teeth. Decay rate can be modified by hereditary and environmental factors including genetic susceptibility, exposure to fluoride, diet, and oral hygiene practices.

Hawaii represents a good area for such a study because the level of fluoride is consistently low and, therefore, environmental protection against tooth decay is ruled out. Also, several races live together in Hawaii under quite similar circumstances.

Jean H. Hankin, D.P.H.; Chin S. Chung, Ph.D.; and Manuel C.W. Kau, D.D.S.; of the University of Hawaii, and the Hawaii State Department of Health, compared 910 eighth grade students from three schools in Oahu. The pupils of one were predominantly of Hawaiian ancestry; of another, Japanese; of the third, Caucasian.

The children were asked on successive days (Monday, Tuesday, and Wednesday) to recall what and how often they had eaten during the preceding

(more)

Tooth Decay (Cont'd)

24 hours. (This would therefore include one weekend day and two school days.) The foods were then grouped in eight categories: bread and cereals; meat, fish, poultry; starchy foods; vegetables; beverages; desserts; snacks; candy, and gum.

After the dietary surveys were completed in each school, a dentist examined each child and recorded the number of decayed, missing, and filled teeth. A record was also made of the age, sex, years of residence in Hawaii, race, parental occupation, and tooth brushing habits of each child.

The findings from the survey reveal that the longer the child had lived in Hawaii, the more decay he or she suffered. The investigators attribute this to the lack of fluoridation in the water. However, frequent, regular brushing could inhibit this effect.

Also, the investigators found the frequency of candy eating and gum chewing to be positively correlated with decay, while frequent eating of bread and cereal correlated with less decay.

As expected, the Caucasian group was characterized by a higher frequency of intake of bread and cereal in comparison with other racial groups. The Hawaiians eat more starchy foods, sweet beverages, desserts, snacks, candy, and gum.

The observation from the study that boys had significantly less dental caries than girls is consistent with previous reports.

All racial variations in decay could not be accounted for by such factors as the Hawaiians greater fondness for sticky starches and sweets and their life-long deprivation of fluoride. The investigators do not know at

(more)

Tooth Decay (Cont'd)

this time whether the difference is genetic or due to some unknown environmental factors.

The investigators reported their findings in the *Journal of Dental Research*, Part 2, September-October 1973.

#

MIDDLE EAR--Inflammation of the middle ear space can lead to conductive hearing loss by blocking sound which must pass through the middle ear to the inner ear where it is processed and sent to the brain, according to the National Institutes of Health.

ENDOCRINOLOGY--Endocrinology, the study of the internal glandular secretions of the body, is an immense biomedical field which directly pertains to important life functions, such as growth, metabolism, and reproduction, according to the National Institutes of Health.

FOOD ALLERGIES--The most common food allergies are to fish, berries, nuts, eggs, cereals, milk, pork, chocolate, beans, and various fresh fruits. The National Institutes of Health reports that some people are also allergic to such substances as food additives.

Research Advances

IN THE LITERATURE:

Cleft Palate Journal, July 1973

STUDY COMPARES PARENTS WITH CLEFTS AND SIBLINGS--In an effort to learn the relative ability of adults with facial clefts to get along in the world, scientists have compared parents, nearest non-cleft siblings, and 115 cleft individuals (age 18-38) as to marital status and levels of education and occupation.

Their findings show that the greatest difference was in marital status. Only 40 percent of the cleft adults married while 72 percent of their nearest siblings did so.

Cleft and non-cleft children reached significantly higher educational levels than their parents, quite in line with current educational trends in this country. However, the investigators were surprised to find that the children's occupations were essentially equivalent to those of their parents and did not reflect their improved educations.

The educational drop-out rate of cleft children was similar overall to that of their siblings. However, cleft subjects tended to leave school earlier than their non-cleft siblings in families whose educational pattern did not include completion of high school. In families with a college tradition, cleft and non-cleft subjects reached similar educational levels.

Betty Jane McWilliams, Ph.D., and Leone P. Paradise, M.S., of the University of Pittsburgh Cleft Palate Center, think that a clue to the unexpected finding that ~~occupations~~ did not improve proportionately with better education was revealed by parents' answers to an invitation to discuss any question they might have. A number of mothers feared that the

(more)

Cleft Palate (Cont'd)

attention required by the cleft child had shortchanged the nearest siblings to some extent. This might account for their slower progress.

This finding, together with the unfavorable marital status of cleft individuals, suggests to the investigators that more family counseling may be needed to help both cleft and normal children in a family to achieve their full social potential.

This research was reported in the *Cleft Palate Journal*, July 1973. The work was supported by the National Institute of Dental Research.

#

CHOLESTEROL--Elevated blood levels of cholesterol and other fatty substances (collectively called lipids) are often strongly associated with increased risk of premature arteriosclerosis and coronary heart disease, according to the National Institutes of Health.

HODGKIN'S DISEASE--Recent developments in the treatment of Hodgkin's disease, a form of cancer affecting the lymphatic system, indicate that most patients treated in the early stages can be cured, according to the National Institutes of Health.

Photo Feature

NCI STUDIES PARTICLES
OF CIGARETTE SMOKE

The National Cancer Institute (NCI) owns four special machines that are heavy smokers.

Each machine can smoke up to 2,000 experimental cigarettes per hour during studies of the possible hazards of smoke components.

The smoking machine has a glass trapping system that collects the same particles normally collected in the lungs of human smokers. A condensate extracted from the residue is studied in hopes of determining which of hundreds of smoke components are harmful to humans.

An ultimate goal of the research is the development of a recipe for a less hazardous cigarette.

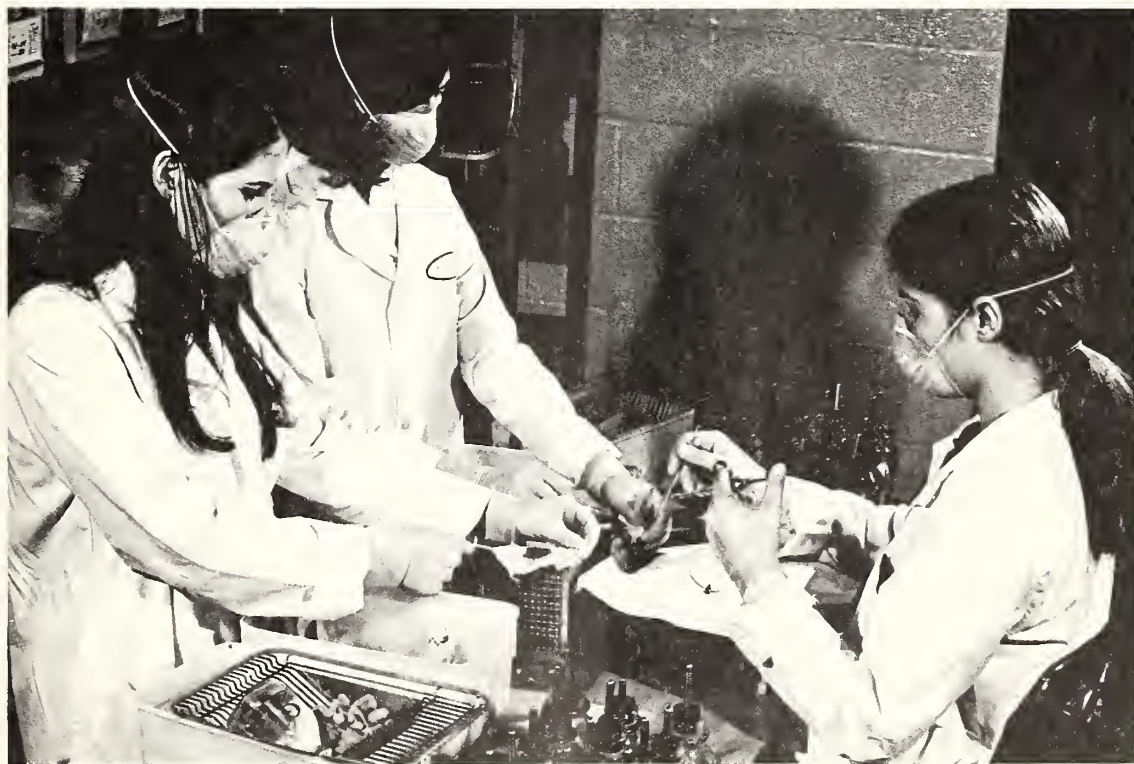
(more)



This smoking machine, one of four being used in a NCI research project, can smoke up to 2,000 cigarettes an hour. Tests of smoke components may lead to suggestions for ways to make a less hazardous cigarette. Meloy Laboratories, Springfield, Virginia, is operating the machines. (NIH Photo #1191)

Cigarette Smoke (Cont'd)

Tobacco plants grow in a water and chemical solution before they are made into experimental cigarettes to be smoked by a special machine. T.C. Tso, Ph.D., above, heads the tobacco growing studies at the U.S. Department of Agriculture facilities in Beltsville, Maryland (NIH Photo #1192)



Technicians paint the skin of thousands of white mice with components of cigarette smoke. Scientists under contract to NCI have found that the more tar present in the smoke particles, the more tumor produced in the animals. (NIH Photo #1193)

News Feature

USHER'S SYNDROME BRINGS
DEAFNESS, LOSS OF VISION

National Eye Institute (NEI) scientists are studying Usher's syndrome, the genetic disease resulting in deafness and retinitis pigmentosa (a slowly progressive loss of night and side vision). Although hearing difficulty frequently occurs in adult patients who have retinitis pigmentosa, Usher's syndrome is distinguished by the presence of profound, congenital deafness.

The frequency of Usher's syndrome is very low in the general population, occurring among approximately four percent of the profound congenitally deaf population. However, the incidence may be higher because the signs and symptoms of retinitis pigmentosa may not be present or detected until after school age.

The onset of visual difficulty may occur from childhood to middle age, with the night blindness beginning many years before the loss of side (peripheral) vision is disabling. The central (reading) vision is generally maintained for many years after extensive loss of peripheral vision has occurred.

The symptoms of retinitis pigmentosa are: night blindness (poor dark adaptation) which is usually present to some extent from childhood but usually does not bring the patient to the doctor; poor side vision (visual field loss) which is usually detectable at adolescence; poor central vision which is usually not a problem until late in life. These symptoms often will be manifest in the deaf individual indirectly, for example, by missing hand or gesture communication in groups or experiencing difficulty with

(more)

Usher's Syndrome (Cont'd)

school work due to decreased reading speed.

There are several tests for retinitis pigmentosa. The diagnosis is usually detected by observation of pigment clumping and narrowing of blood vessels inside the eye. Such detection depends heavily on dilation of the pupil with medication, because not all areas of the retina are equally involved and the signs may be missed if dilation is not used.

A second test, dark adaptation, measures the dimmest light that can be seen after entering a dark room. Normally there is a rapid increase in ability to see the dim light (increasing sensitivity, decreasing threshold) during the first 20 minutes in the dark. Retinitis pigmentosa produces slow and incomplete dark adaptation. Since not all areas of the retina are affected mild cases occasionally could go undetected unless the test is administered so as to check specified areas of the retina.

Visual field testing detects a loss of peripheral vision which typically begins in the mid-periphery producing a donut shaped area of poor vision ("ring scotoma"). Later, in severe cases, only the very central vision and frequently a peripheral island of vision remain.

A fourth test for retinitis pigmentosa is the electroretinogram (ERG). The ERG measures the electrical potential produced by the retina and the pigment epithelium in response to light. (It is diminished or absent in retinitis pigmentosa.) This test is extremely helpful in detecting early cases when such information is desirable for definitive diagnosis of unusual cases or for genetic counseling.

The prognosis of a patient must be individualized depending on the

(more)

Usher's Syndrome (Cont'd)

specific findings in each case. If an older family member has been affected, this may serve as a general but not precise guide as to the expected course of the younger patient. The general prognosis is one of slow progression over many years.

Rehabilitation of visually handicapped individuals often begins when they reach the level of legal blindness, (visual acuity of 20/200 or worse in the better eye or less than 20 degrees of horizontal field). However, the double handicap of profound deafness and poor vision is much greater than the sum of the single handicaps. The patient with Usher's syndrome will, therefore, require rehabilitation at a somewhat earlier stage of visual loss than will the hearing individual with isolated retinitis pigmentosa. Deaf-blind rehabilitation training should be started before the patient is totally handicapped visually.

At present, rehabilitation for loss of night and peripheral vision is best accomplished with mobility training, such as the long white cane technique. Rehabilitation for patients with loss of field to the extent that reading and visual hand signal communication are impaired requires tactile communication training. Furthermore, there are many techniques which make daily activity easier for the trained deaf-blind or deaf-partially sighted individual.

There is not known effective treatment for preventing visual loss in retinitis pigmentosa nor for restoring retinal function once it is lost. However, some patients are aided by visual aids depending on the status of their central and peripheral vision and on their specific visual needs. In

(more)

Usher's Syndrome (Cont'd)

addition, a large percentage of patients with retinitis pigmentosa eventually develop cataracts and, their removal may result in improved vision for the patient despite partial loss of retinal function from retinitis pigmentosa.

Prevention of the disease can be accomplished to a small degree by genetic counseling. It is important that patients with Usher's syndrome be identified and given genetic counseling, particularly since they run a high risk of meeting friends carrying the same genetic defect at schools for the deaf.

Screening programs for Usher's syndrome would best be directed at the appropriate deaf populations at the high school level. This would allow children with the disease to learn as much visually as possible and also allow time for proper occupational decisions to be made. Individuals who develop signs or symptoms of the disease at earlier or later ages can be referred for ophthalmologic examination without screening programs.

This description of Usher's syndrome was made by Donald Bergsma, M.D., an NEI researcher, at a conference on Usher's syndrome at Galludet College in Washington, D.C., April 1973. Dr. Bergsma and other NEI scientists are conducting research on retinitis pigmentosa and other degenerative retinal conditions.

Photo Feature

CONNECTICUT SCIENTISTS CONDUCT
NUCLEAR MOLECULE STUDIES

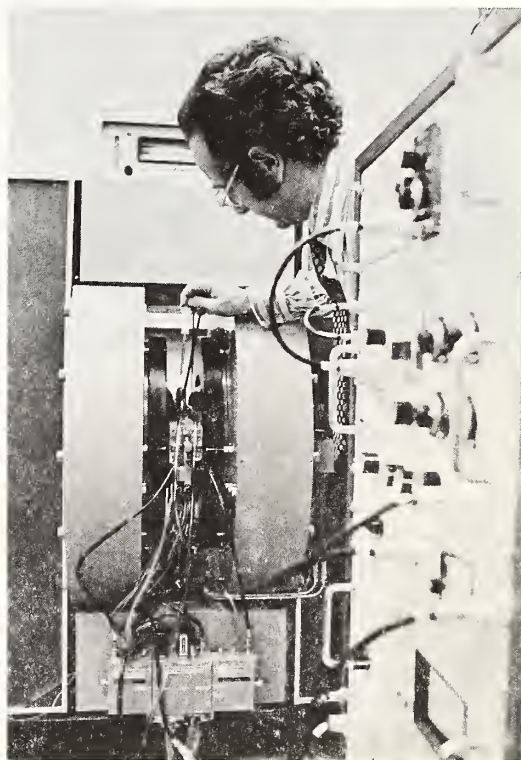
Scientists at the University of Connecticut Health Center are now operating a nuclear magnetic resonance (NMR) spectroscopy laboratory, one of the most advanced methods of probing the secrets of life on the molecular level.

The laboratory, funded by NIH's Division of Research Resources, will serve research scientists throughout New England, giving them new opportunities to decipher the structure and conformation of molecules.

NMR works by causing the nuclei of molecules to resonate in a magnetic field and produce signals. Analysis of these signals and their different frequencies enables scientists to build up a picture of the whole molecule.

According to Jay A. Glasel, Ph.D., associate professor of biochemistry and principal investigator at the NMR lab, the NMR spectrometer facility is one of the most powerful in the country.

"It is an invaluable tool," he said, "for finding the structure and shape of molecules and learning how they interact.



Dr. Jay Glasel inserts sample to be studied in magnetic field. (NIH Photo #1194)

(more)

Molecule (Cont'd)

In combination with computers, it can reduce analysis time from months to several days."

One of the three small computers in the laboratory translates data about a molecule into a three-dimensional picture of its most probable structure. The picture, displayed on a video terminal, consists of a pair of stereoptic views. To practiced eyes, these converge into a 3D image.

Dr. Glasel's major research interest is in applying NMR spectroscopy to biophysical problems such as membrane structure. He is also studying hormones and hormone releasing factors. Their structures, he believes, will show how they work.



Dr. Albert Kung (right) and Dr. Jay Glasel view a molecule on the 3D video computer terminal. (NIH Photo #1195)

#

GOUT--Victims of gout can now be taken care of with reasonable comfort and can be assured that their disorder, if diagnosed early and treated properly, will not cripple them, according to the National Institutes of Health.

Medical News Tip

FERTILITY STUDIES--Data drawn from the two National Fertility Studies reveal a dramatic drop in unwanted fertility in the United States. The studies were supported by the Center for Population Research of the National Institute of Child Health and Human Development (NICHD).

Between 1961-65 and 1966-70, an overall decline of 36 percent in the number of unwanted births per 1,000 woman-years of exposure to the risk of unwanted pregnancy occurred. For whites, the decline was 35 percent; for blacks, 56 percent. The studies were based on interviews conducted with samples of 4,810 (1965) and 5,884 (1970) married women under 45 years of age.

Although there was little change in the proportion of couples currently using contraception, significant changes in methods of fertility control by couples were apparent. Voluntary sterilization became the most popular means of fertility control for couples in which the wife was between 30 and 44 years of age. The operations were equally divided between men and women.

Oral contraceptives were by far the most popular means of fertility control. Use among young black women increased the most between 1965 and 1970.

Although the popularity of the IUD is still well below that of oral contraceptives, 7.4 percent of women were using it in 1970 as compared to 1.2 percent in 1965. Use of most other methods of fertility control--the condom, diaphragm, rhythm, withdrawal, and douche--declined.

For additional information about these studies, contact: NICHD, Landow Building, Room A-804, Bethesda, Maryland 20014, Phone (301) 496-5133.

Capsules

Research Illustrated



M. Ashton Barfield, Ph.D., is injecting progesterone into a rabbit to study the hormone's effect on the production of uteroglobin, a protein produced by the uterus under the influence of progesterone. Uteroglobin may be important for the maintenance of the embryo prior to implantation and possibly for implantation. Around implantation, the protein seems to disappear. Dr. Barfield is trying to determine the cause of uteroglobin disappearance. Prevention of secretion of the protein might serve as an anti-fertility technique. Dr. Barfield is a postdoctoral trainee in reproductive biology at the University of Pennsylvania School of Medicine. Her research is part of a project supported by the National Institute of Child Health and Human Development. (NIH Photo #1196)

New Publication:*Do We Care About Research Animals?*

The Division of Research Resources (DRR) has released a new publication, *Do We Care About Research Animals?*, explaining the importance of animals in research and explaining the care given to these animals.

Today, hundreds of thousands of people owe their health and their lives to medical research, much of which was initiated using laboratory animals. Since it is too dangerous to administer a previously untried drug or attempt an untested surgical procedure on a human patient, medical scientists use animals whose basic life processes resemble man's to make useful conclusions about the effects of the new drug, surgery, or other therapy.

DRR's Animal Resources Branch conducts a full-scale program to aid laboratory animals and to assist scientists in using new research animals. This branch trains professional and technical personnel to give the best possible care to research animals.



Science writers can obtain a free copy of this publication from:

Office of Science and Health Reports
Division of Research Resources
National Institutes of Health
Building 31, Room 5B-39
Bethesda, MD 20014
Phone: (301) 496-5545

NEWS & FEATURES From NIH

January 25, 1974

News Releases Issued

SMOKING & HEALTH--NCI and the National Clearinghouse for Smoking and Health have pooled resources in the effort against lung cancer and related diseases. NCI's Cancer Control Program, through a service agreement, will transfer \$1,665,000 to the Clearinghouse this year to support educational programs designed to reduce the number of Americans who smoke; reduce the number of young Americans who acquire the habit; minimize hazards to those who continue to smoke. The agreement will permit continuation and expansion of Clearinghouse education programs to inform health professionals, community organizations, students, and the general public about the dangers of smoking.

#

January 24, 1974

Editors of publications may request glossy prints of numbered photographs that appear in the regular issue.

NEWS & FEATURES From NIH
National Institutes of Health
Building 31, Room 2B-10
Bethesda, MD 20014

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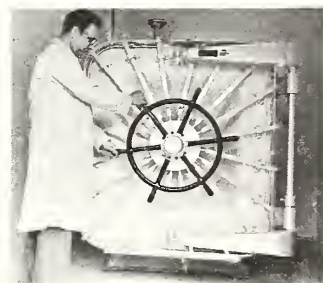
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NEWS & FEATURES ^{FROM}

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February 10, 1974



See page 11

	<u>Page</u>
RESEARCH ADVANCES:	
Primary Teeth Reveal Exposure to Lead.....	1
Chemical Treatment Effective in Hereditary Bone Disease.....	4
Scientists Grow Human Heart Cells.....	8
NEWS & PHOTO FEATURES:	
New Isolation Facility Provides Safer Research.....	11
Heart-Lung Machines Improve Cardiac Surgery.....	13
New Nuclear Scanning Technique Pinpoints Heart Attack Damage.....	17
MEDICAL NEWS TIP:	
Divorce.....	20
CAPSULES:	
Research Illustrated.....	21
NEWS RELEASES ISSUED:	
Nicotine, Asthma & Allergy, Associateships.....	22

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Bethesda, Maryland 20014
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Research Advances

PRIMARY TEETH REVEAL
EXPOSURE TO LEAD

An analysis of lead accumulation in primary teeth has revealed that children living near lead-processing industries or heavily-trafficked thoroughfares may be exposed to dangerous levels of lead. Experts hope to determine the long-term effects of lead exposure, by comparing lead levels in a child's exfoliated primary teeth with his behavior.

Herbert L. Needleman, M.D., of the Children's Hospital Medical Center, Boston, and Irving M. Shapiro, D.D.S., Ph.D., of the University of Pennsylvania's Center for Oral Health Research, Philadelphia, report that measurement of lead in the teeth that children shed is an excellent way to determine long-term lead exposure.

Severe lead poisoning usually occurs in young children who have nibbled chips of peeling lead-based paint found in many old houses. Central nervous system damage and even death may result. Acute lead poisoning can be detected by measuring levels of lead in the blood, but the technique is not always reliable for measuring low levels. Furthermore, because blood levels decline after exposure ceases, blood determinations do

(more)



Dr. Irving M. Shapiro analyzes the lead content of teeth in a solution with the aid of an atomic absorption spectrophotometer. (NIH Photo #1197)

Teeth (Cont'd)

not reflect accumulation from long-term exposure.

An earlier study by Drs. Needleman and Shapiro revealed that teeth from children in urban Philadelphia had five times as much lead as suburban children's teeth. Lead accumulates in secondary dentin adjacent to the pulp, where tissue is laid down continuously until the tooth is shed. Therefore, dentin can indicate cumulative exposure. (See *NEWS From NIH*, February 15, 1972.)

In the current study, the investigators found high concentrations of lead in the dentin of teeth from children living in areas with deteriorating old houses; 20 percent of these black public school children had levels in the range associated with toxicity (above 300 micrograms).

Surprisingly, white children living nearby in housing which was generally in a better state of repair also had similar levels. These children attend a parochial school that is adjacent to a paint manufacturer and synthesizer of lead stearates for plastic fabrication. Their school district is bounded by a major six-lane highway with other major roadways paralleling or crossing it.

To study possible contamination from the lead processing factory or from leaded gasoline emissions, the investigators analyzed dust from the schoolrooms, gutters, as well as soil samples from the schoolyards. As expected, they found more lead in the city schools than in a suburban school located away from heavy traffic and industry.

Lead-bearing dust can be swallowed or inhaled and absorbed from the lungs. Drs. Needleman and Shapiro estimate that ingestion of only 75 mgm

(more)

Teeth (Cont'd)

of lead-bearing dust could result in the daily permissible lead intake for children--300 micrograms per day. Such lead pollution would increase the toxic burden of children living in deteriorating houses.

Not only does this study reveal that many more children may be at risk of damage from lead contamination than was previously suspected, but it also underscores the value of using teeth for diagnosing lead burden. The investigators hope to learn what levels of lead in teeth indicate a danger of chronic poisoning by correlating their measurements with tests of behavior, learning, and neurologic function.

This research, which was funded in part through the National Institute of Dental Research's support of the Pennsylvania Center for Oral Health Research is described in January 31, 1974 *New England Journal of Medicine*.

#

BRONCHITIS--In chronic bronchitis, there is persistent inflammation of the smaller air tubes in the lungs. The onset of the disease may be slow, according to the National Institutes of Health.

EMPHYSEMA--In emphysema, stale air becomes trapped in the lungs, according to the National Institutes of Health. In the early stages of the disease, only a small amount of air is trapped and the effect is hardly noticeable. As the disease progresses, more air is trapped and less healthy tissue remains in contact with the blood.

Research Advances

Osteogenesis Imperfecta...

CHEMICAL TREATMENT EFFECTIVE
IN HEREDITARY BONE DISEASE

A new chemical approach appears to be effective in the treatment of osteogenesis imperfecta, a hereditary, crippling bone disease in children. The drug involved is a synthetic version of calcitonin, a hormone produced by the thyroid gland.

Salvador Castells, M.D., associate professor of Pediatrics at Downstate Medical Center, Brooklyn, New York, and head of the four-member research team conducting the study, believes that calcitonin has demonstrated its potential as a safe, effective treatment that might help to arrest the development of this severely disabling disease. Dr. Castells is a major investigator at the General Clinical Research Center in Brooklyn. The Center is supported by the NIH Division of Research Resources.

Children suffering from osteogenesis imperfecta may break an arm or leg a dozen times a year because of minor accidents. The disease causes generalized decalcification of the skeleton, with the resulting softness and porosity leading to multiple fractures and severe deformities such as curvature of the spine, hunchback, and legs of uneven length.

Children with osteogenesis imperfecta usually remain small in stature. (Toulouse Lautrec, the French artist, may have had this disease.) Many also have markedly blue eyes because of the blue coloration of the sclera, or covering of the eyeball. Softening of the inner bones of the ear frequently causes deafness.

The basic mechanism underlying the disease seems to be overactive calcium resorption. Bone formation proceeds normally, with adequate supplies
(more)

Osteogenesis Imperfecta (Cont'd)

of calcium produced and delivered via the blood vessels to the bones. However, the timing appears to be faulty. Calcium resorption by the blood occurs at a faster rate than calcium accretion, and therefore the calcium does not remain in the bone long enough for calcification and growth to take place.

Calcitonin appears to retard the flow of calcium from bone to blood. Its effectiveness in the treatment of Paget's disease and osteoporosis, two conditions also characterized by high bone resorption rates, led Dr. Castells and his group to investigate the effect of the hormone on pediatric patients with osteogenesis imperfecta.

(more)



Kelli-Jo Christie paints in the playroom at Downstate Medical Center where she is under treatment for osteogenesis imperfecta. Only three years old, Kelli-Jo had broken bones four times before she entered Downstate for evaluation and treatment with a new drug. Salvador Castells, M.D., is studying the effectiveness of the drug in treating the disease. (NIH Photo #1198)

Osteogenesis Imperfecta (Cont'd)

Three girls and two boys (ranging in age from four years two months to thirteen years) with osteogenesis imperfecta tarda--a form of the disease that usually manifests itself when the child begins to walk--have been admitted to a metabolic ward of the Clinical Research Center in Downstate's State University Hospital.

The children received injections of synthetic salmon calcitonin three times a week for six weeks. Calcium balance and radioactive calcium studies of the young patients were performed before and during the short-term calcitonin therapy.

According to Dr. Castells, the clinical and metabolic effects were encouraging. "The data indicate that calcitonin, probably through its ability to inhibit skeletal resorption, reduced skeletal turnover and thereby increased calcium accumulation by the skeleton."

The hormone was effective in increasing positive calcium balance and in reducing bone turnover in the skeletons of these children, suggesting to the investigators that long-term calcitonin therapy may help suppress the flawed metabolic processes underlying osteogenesis imperfecta. The researchers noted also that there were no adverse reactions, toxic effects, or allergic responses to the calcitonin.

Dr. Castells believes that calcitonin's "suppressing" or holding action is significant in the treatment of the child with osteogenesis imperfecta, since it can be used without unpleasant side effects, therapy can be started at an earlier stage of the child's development, before fractures

(more)

Osteogenesis Imperfecta (Cont'd)

and deformities occur, giving him a chance to grow normally.

Patients treated with calcitonin seem to break fewer bones, experience a temporary spurt in growth, and show some increase in bone density. "If you can reduce the number of fractures and improve the density of the bone," says Dr. Castells, "these alone are really significant improvements in the management of these patients."

To date, five children have gone through two-week to eight-week treatment courses at Downstate. They will continue the calcitonin regimen and come to the hospital for a checkup once a month--or every three months, if they live outside the city--until they reach puberty, when the disease will seem to disappear. In postmenopausal women, the tendency to osteoporosis and fracture will reappear.

Dr. Castells published a full report of his findings in *Current Therapeutic Research*, January 1974.

#

TINNITUS--Aggravating head noises known as tinnitus are one of the most common complaints of persons with ear disorders. This condition is characterized by either a high-pitched whistle or a low-pitched roar. Doctors say these sounds indicate that the entire inner ear is being irritated. Possible causes are numerous, according to the National Institutes of Health.

Research Advances

SCIENTISTS GROW
HUMAN HEART CELLS

Scientists at the University of Chicago have developed methods for the isolation, growth, and replication in the laboratory of adult human heart cells. These studies appear to duplicate previous work by the investigators in growing heart cells from adult rats.

According to Donald A. Fischman, M.D., associate professor in the Departments of Biology and Anatomy, this research may lead to improved methods for regenerating heart muscle after heart attacks or cardiac surgery. The research also may aid in the establishment of heart cell banks where cardiac surgeons can draw healthy muscle to replace dead or scarred tissue.

Based on existing evidence that human, rat, or chicken heart muscle cells cease to divide soon after birth and fail to regenerate new muscle in the adult after injury, Dr. Fischman and associates developed methods for growing chick heart cells in the laboratory, either as isolated cells or in cellular reaggregates known as organ cultures.

When cultured as single cells, cellular division, DNA synthesis, and the levels of a crucial enzyme (DNA polymerase) increase. Upon reaggregation of the cells, mitosis falls and there is an increased formation of muscle myofibril proteins required for heart contractions, according to Dr. Fischman.

Using adult rat and human heart cells Dr. Fischman and associates adapted methods developed by other investigators to disperse ventricular adult rat and human muscle into single cells utilizing collagenase and hyaluronidase. (Such cells are perfectly viable and continue to contract in a test tube.)

(more)

Human Heart Cells (Cont'd)

Then, they established cultures based on their experiences with chick embryos. After several days, the muscle cells attached to the Petri plate and sent out pseudopodia which resemble similar protrusions from amoebae.

According to Dr. Fischman, these cytoplasmic extensions of the muscle cells appear to lack contractile proteins, but contained the nucleus and other cellular organelles necessary for life.

Dr. Fischman explains that once devoid of myofibrils (the contractile machinery), these cells reinitiate DNA synthesis and cell division. The heart cells, while attaching to the substrate, actually eliminate their contractile proteins and then commence cell division.

According to the investigators, some caution must be exercised in interpreting these results. The work is still in progress and all of the tests necessary to eliminate the possibility of a small inclusion of cells from the blood vessel wall and connective tissue in the muscle cell preparation have not been completed.

However, the results with human hearts are fully consistent with the prior rat studies. Both investigations suggest that adult heart muscle may be cultured in the laboratory and under such conditions can reinitiate cell division.

According to Dr. Fischman, the assumption that damage to heart muscle in myocardial infarction is irreversible may not be the case. "Perhaps the repression of DNA synthesis and mitosis in adult heart muscle is not irreversible. If this regulatory mechanism could be manipulated by the physician, one might be in the position to restore damaged heart muscle after

(more)

Human Heart Cells (Cont'd)

a heart attack."

Dr. Fischman was assisted in his work by Ashish C. Nag, Ph.D., Murray Rabinowitz, M.D., Radovan Zak, Ph.D., Robert Replogle, M.D., Yutaka Shimada, M.D., Aron Moscona, Ph.D., and Catherine Doyle, Ph.D. Dr. Nag provided the photomicrographs of the adult heart cell experiments.

Dr. Fischman presented a report of his findings at the American Heart Association Science Writers Forum at Marco Island, near Naples, Florida, January 21, 1974. His work was supported by the National Heart and Lung Institute.

#

MS--In the United States, multiple sclerosis is more common across the northern portions than in other parts of the Nation. It is more frequently encountered in Canada and the northern countries of Europe than in the hot Mediterranean basin, according to the National Institutes of Health.

CRYOSURGERY--Cryosurgery is a surgical technique employing the use of extreme cold for such purposes as reattaching detached retinas and removing cataracts, according to the National Institutes of Health.

DIABETES--Diabetes develops in people in all age groups, according to the National Institutes of Health. However, those who are most likely to have the disease are: overweight, over forty, relatives of diabetics, mothers who give birth to babies over nine pounds.

Photo Feature

At Delta Regional Primate Research Center...

**NEW ISOLATION FACILITY
PROVIDES SAFER RESEARCH**

The new special isolation facility for infectious disease research at the Delta Regional Primate Research Center, Covington, Louisiana, gives the Center a unique capability among the seven primate research centers supported by NIH's Division of Research Resources.

As scientists work with highly infectious agents, the new facility provides exhaustive safeguards to prevent the spread of viruses, bacteria, and other microorganisms.

The flow of air within the isolation facility travels from the outside toward a filter bank which is 99.99 percent effective.

Equipment in the new facility includes an autoclave for sterilization and decontamination large enough to accommodate an animal cage, as well as air-tight special isolation cages that enable researchers to eliminate the problem of cross contamination.

Particularly hazardous materials may be studied in special biological containment cabinets that feature either negative pressure (in which air



Bruce Golden, M.D. (left), and Robert Lowrie, Ph.D., collect conjunctival cells from the eye of an owl monkey in keratoconjunctivitis studies. (NIH Photo #1199)

(more)

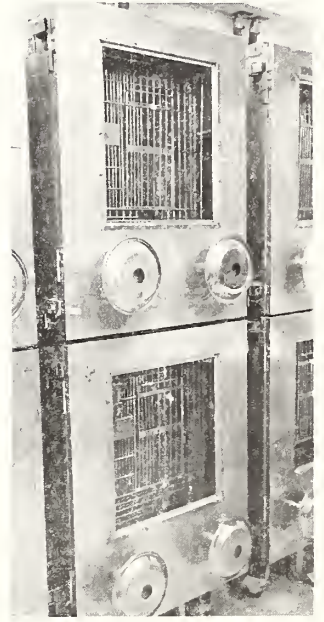
Isolation (Cont'd)

moves from the experimenter into the cabinet) or a laminar airflow curtain, which serves as a screen between inside and outside air.

According to Peter Gerone, Sc.D., director of the Center, the new facility protects one scientific experiment from contamination by a virus being studied in another, as well as providing safety for the researchers.

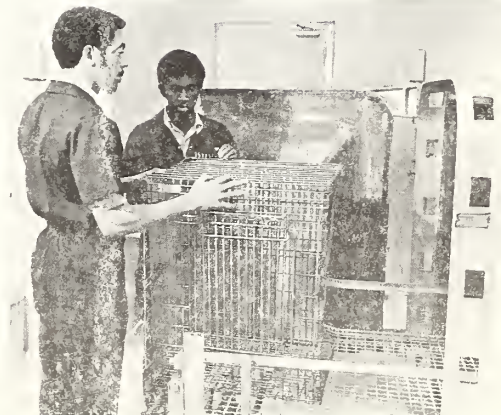


Peter Gerone, Sc.D. (left), Center director, and William P. Allen, Ph.D., work at the laminar-flow cabinet (NIH Photo #1201)



Air-tight special isolation cages at the new facility prevent cross contamination. (NIH Photo #1200)

When an animal cage becomes contaminated, vivarial assistants (right) place it in a large autoclave, where it remains overnight for complete sterilization. (NIH Photo #1202)



News Feature

HEART-LUNG MACHINES
IMPROVE CARDIAC SURGERY

During recent years, the treatment of inborn defects of the heart and great vessels has become increasingly effective. Corrective or palliative operative procedures have been devised for most types of congenital heart defects, including all of the most common forms.

Among affected infants or children who would stand little or no chance of survival without surgery, the salvage rate currently ranges from better than 80 percent to nearly 100 percent for the most common types of congenital heart disease. Surgical risk is still high for very young infants with complex or multiple defects, but is extremely small in older children with simple defects.

Similarly, surgery to repair or replace heart valves damaged by rheumatic fever has improved substantially. Today, surgeons undertake the replacement of one, two, and even three diseased heart valves in a single operation with high expectations that the patient will survive due to improved surgical techniques and a variety of clinically proven artificial heart valves developed within the past decade. Equally important to the success of surgery for treating congenital heart disease, rheumatic heart disease, and other heart disorders have been advances in heart-lung machines and other life-support techniques for sustaining the patient during prolonged open-heart operation.

Ingenuous techniques for repairing certain heart defects were developed during the 1940's and 1950's. However, before surgeons could undertake the

(more)

Heart-Lung Machines (Cont'd)

correction of any but the simplest heart defects, they had to learn how to sustain life during direct-vision surgery in widely opened, stilled hearts. The development of two such life-support techniques--hypothermia and extracorporeal circulation--has made such surgery possible and has paced most of the progress in this field.

Hypothermia, or total body cooling, slows body metabolism and reduces the oxygen requirements of the tissues, so that the heart and brain can tolerate short periods of interrupted bloodflow. The technique was first used clinically in connection with heart surgery in 1953.

In the early days of hypothermia, the anesthetized patient was chilled by the simple expedient of immersing him in ice water. Later he was placed in a water jacket through which cold saline was circulated. Reducing body temperature by some 10-15 degrees Centigrade permitted the heart to be stopped safely for about six to eight minutes--insufficient for the repair of any but the simplest defects.

To gain enough time within the stilled, non-functioning heart to attempt the repair of more complicated defects, surgeons turned to extracorporeal circulation. In this technique, blood bypasses the heart and lungs completely. It is pumped and oxygenated by a heart-lung machine located outside the body.

Dr. John Gibbon of Jefferson Medical College, Philadelphia, was a pioneer in the development of concepts and techniques of extracorporeal circulation. In 1953, his work resulted in the first successful use of a heart-lung machine to maintain heart and pulmonary function during open-

(more)

Heart-Lung Machines (Cont'd)

heart surgery.

In the "lung" of Dr. Gibbon's machine, blood was filmed over stainless steel screens in an atmosphere rich in oxygen. Although the basic design of the machine was sound, many problems remained to be solved before it could be used with consistent success in heart surgery.

However, during this period scientific interest in extracorporeal circulation was sustained by a series of accomplishments by Dr. C. Walton Lillehei and co-workers of the University of Minnesota.

The first of these was the development and clinical application of controlled cross-circulation of blood between the patient and a healthy donor (usually a parent) to achieve heart-lung bypass. During the year during which the technique was used clinically, it made possible the repair of complicated, formerly incurable congenital defects in 26 patients.

This technique also established a physiological principle of great importance to subsequent research in extracorporeal circulation: the "low-flow" principle. The scientists showed that fairly long periods of reduced bloodflow can be tolerated without harm to the patient. This finding greatly simplified problems in the design of heart-lung machines.

Using this principle, the scientists subsequently developed a disposable artificial oxygenator where oxygen bubbles, rising through a blood-filled plastic chamber, revitalized the blood by diffusion. This bubble oxygenator, along with de-bubbling devices and mechanical pumps, was incorporated in 1956 into the first heart-lung machine found consistently satisfactory for open-heart surgery.

(more)

Heart-Lung Machines (Cont'd)

This and other oxygenators developed during this period brought the blood into direct contact with a high-oxygen atmosphere. Subsequent studies showed that such direct blood-gas contact damaged the red blood cells and plasma proteins. The next major innovation was the membrane oxygenator, in which the blood was protected from direct contact with the oxygen-rich atmosphere by a thin plastic membrane. The membrane was permeable to oxygen and to carbon dioxide, and gas exchange took place across the membrane in much the same way as it occurs in the human lung.

Most oxygenators used in heart-lung machines today are membrane oxygenators. New developments in materials and oxygenator design have been chiefly concerned with improving the gas-exchange efficiencies and blood-handling characteristics of membrane oxygenators while reducing their size.

Once hypothermia and extracorporeal circulation had demonstrated their individual worth in cardiovascular surgery, surgeons attempted to capitalize on the advantages of both. The combination of hypothermia with low-flow heart-lung machines at last provided the surgeon with direct-vision access to the stilled heart for periods long enough to correct even the most complicated defects.

Another innovation was the incorporation of a heat exchanger into the heart-lung circuit to induce hypothermia by direct cooling of the blood. This technique is far more efficient in reducing the oxygen needs of the patient than is immersion hypothermia because those tissues requiring the most oxygen will be cooled most rapidly.

Photo Features

NEW NUCLEAR SCANNING TECHNIQUE
PINPOINTS HEART ATTACK DAMAGE

For the first time, doctors can see the exact area of damage caused by a coronary heart attack.

With a new nuclear scanning technique developed by Frederick J. Bonte, M.D., dean of The University of Texas Southwestern Medical School, physicians can view and take a picture of a myocardial infarct. Armed with this new tool of diagnosis, the doctor can determine, usually within an hour, if a person actually has a heart attack or simply pain from other sources. Where the scan shows an infarct, knowledge of its size and position enable faster and more positive treatment.

(more)



Frederick J. Bonte, M.D. (right), demonstrates the new nuclear scanning technique for viewing areas of heart damage. Robert Parkey, M.D., adjusts the scanning screen to illustrate the area of heart death. This research is under way at the University of Texas Southwestern Medical School, Dallas. (The patient is a model.) (NIH Photo #1203)

Nuclear Scanning (Cont'd)

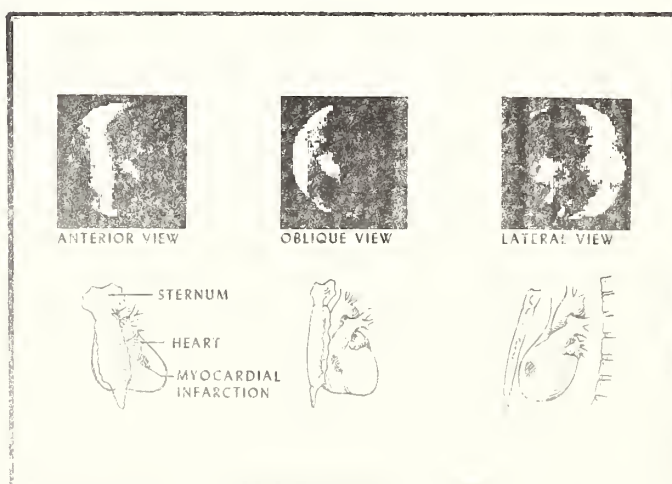
"Until now, the only ways cardiologists had to measure damage from heart attacks were indirect," says Dr. Bonte. With the new method, a radioactive substance with an affinity for calcium is injected into the patient. Within the hour the damaged area of the heart has collected enough calcium tagged with radioactivity to show up as a bright spot on the screen of a scanner, or scintillation camera. The image can be enhanced by computer processing and can be stored on videotape for later replay.

"This is going to be extremely important for clinical cardiology and, what's more, will have great importance in research," according to Jere Mitchell, M.D., head of the Weinberger Laboratories for Cardiovascular Research at Southwestern. He added that knowledge of the size of an infarct could dictate certain courses of treatment.

One advantage of the new technique is that it is an adaptation of some very well known practices used in nuclear medicine to diagnose thyroid tumors and bone tumors. It is, in fact, practically identical to the method used in bone scanning, and knowledge of this method provided Dr. Bonte with the key to the new technique.

(more)

The location and size of a myocardial infarction is shown from three different angles by using the new nuclear scanning technique. Dr. Bonte developed the technique in research supported by the National Heart and Lung Institute. (NIH Photo #1204)



Nuclear Scanning (Cont'd)

Since present scanning equipment is not mobile, access to the coronary care unit is quite limited. The new camera being assembled will have a motorized base so that it can be driven into a coronary unit and pictures in three planes taken with very little disturbance of the patient. The chassis of the unit will contain a small computer which will separate out bone pictures from heart pictures on command or perform other functions to deliver the best looking image.

One important aspect of the discovery is its possible application in other areas of research.

"There seems to be some gradulation of calcium uptake in infarcts--it looks like internal detail," says Dr. Bonte. "Although we have not been able to duplicate this in leg muscle, there may be some possibilities with liver and kidney."

Drs. Bonte and Mitchell are grantees of the National Heart and Lung Institute.

#

INFLUENZA--Unpredictability is one of the key words identifying influenza outbreaks. According to the National Institutes of Health, epidemiologic data have shown that world-wide epidemics (pandemics) have occurred at 10 to 12 year intervals throughout the 20th century.

Medical News Tip

DIVORCE--According to a study supported by the Center for Population Research of the National Institute of Child Health and Human Development (NICHD), divorce in the United States increased by two-thirds between the mid-1950's and 1970, and remarriage rose about one-third.

It is estimated that more than one-fourth of all women near 30 years old have ended or will end their first marriage in divorce. Also, about four-fifths of these women have remarried or probably will remarry.

The divorce rate, remarriage rate and first marriage rate were all at low points during the 1930's, peaked around the end of World War II, and declined during the next decade. However, since the mid-1950's, first marriage rates have continued to decline while the divorce rates and remarriage rates have risen sharply.

Liberalization of divorce laws have probably contributed to the increase of divorce during the 1960's. Also, the rising proportion of women in the labor force indicates that women are generally able to find employment to provide for themselves.

For additional information about this study, contact:

NICHD
Landow Building
Room A-804
Bethesda, MD 20014
Phone (301) 496-5133

Capsules

RESEARCH ILLUSTRATED



A lung function test, known as whole body plethysmography, provides accurate measurements which are of value in asthma and allergy evaluations. Such a test, performed in special booths, is part of research supported by the National Institute of Allergy and Infectious Diseases at the National Asthma Center in Denver. (NIH Photo #1205)

News Releases Issued

NICOTINE--A highly sensitive test to detect nicotine in the blood or urine of smokers has been developed under a research contract awarded by the National Cancer Institute (NCI). The test can detect nicotine, and its principal byproduct, cotinine, in amounts of less than a nanogram (one billionth of a gram). Developed by Dr. Helen Van Vunakis and Dr. John Langone at Brandeis University, the new technique may aid scientists in identifying individuals with a high risk of developing lung cancer, heart disease, or other smoking-related illness. The test will also contribute to NCI research for a less hazardous cigarette.

ASTHMA & ALLERGY--The National Institute of Allergy and Infectious Diseases has added three more institutions to its national network of Asthma and Allergic Disease Centers, bringing the total to 17 Centers. The new Center at Creighton University, Omaha, Nebraska, will study the mechanisms of various pharmacological mediators as they relate to hypersensitivity in the respiratory tract. Investigators at the new Center at Duke University, Durham, North Carolina, will study the basic mechanisms involved in allergy and evaluate the genetic control of allergic diseases. The group at the new Center at the University of Colorado, Denver, will investigate the problem of generalized vasculitis, an inflammation of the blood vessels which may involve immunological factors as the cause or in the disease process.

END OF PAGE

ASSOCIATESHIPS--Young physicians and dentists are invited to apply now for two-year Associateships in clinical and laboratory research at NIH. Designated as Clinical, Research, and Staff Associateships, these positions provide broad opportunities for career development in most of the medical specialties and basic science disciplines. The deadline for receipt of applications is April 5, 1974. Interviews will be conducted June 10 through 21 and successful candidates will be notified of their acceptance on July 8. A 1974 catalog and an application form for the program are available from: Associate Director, The Clinical Center, NIH, Bethesda, MD 20014.

#

CEREBRAL PALSY--Cerebral palsy is not a single disorder, but a group of ailments having a variety of symptoms, according to the National Institutes of Health. All are brain-centered and all affect muscular control.

ASTHMA--Asthma is a remarkably common, noncontagious disease of the lungs. According to the National Institutes of Health, nearly nine million Americans, young and old, are asthmatics.

TB--Improvements in living conditions and the introduction of effective drug therapy have led to a dramatic and steady decline in tuberculosis deaths over the past 25 years, according to the National Institutes of Health.

Editors of publications may request glossy prints of numbered photographs that appear in the regular issue.

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February 25, 1974

See page 10

Page

RESEARCH ADVANCES:

- Combinations of Drugs Reduce Cancer Symptoms.....1
- High-Dose Radiation and Drugs Aid Ewing's Sarcoma Patients.....4
- Study Attempts to Determine Risk for Developing Vaginal Carcinoma.6

NEWS & PHOTO FEATURES:

- Alaska "Winter Walk" Program Simulates Working Conditions.....10
- U.S. Medical Centers Receive Scarce Hormone.....12
- Learning Difficulties Linked With Response to Environment.....14

MEDICAL NEWS TIP:

- Cooley's Anemia.....17

CAPSULES:

- Research Illustrated.....18

NEW PUBLICATION:

- Hepatitis*.....19

NEWS RELEASES ISSUED:

- Sickle Cell.....20

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Research Advances

COMBINATIONS OF DRUGS
REDUCE CANCER SYMPTOMS

Combinations of anti-cancer drugs are proving useful in treating advanced cancers of the breast and ovary, according to scientists at the National Cancer Institute (NCI).

The studies have shown that drug combinations are more effective than single drugs in reducing or eliminating cancer symptoms in women with recurrent and widespread stages of these two cancers. Preliminary results from the NCI studies were reported by Vincent T. DeVita, Jr., M.D., at a Symposium on Combined Modality Therapy of Cancer, February 9, in Denver. The symposium was sponsored by NCI's Division of Cancer Research Resources and Centers and the Cancer Clinical Investigation Review Committee.

Combination drug regimens have led to dramatically improved survival of patients with other forms of cancer, Dr. DeVita noted, including Hodgkin's disease and acute lymphocytic leukemia (the form of leukemia most common in children). These combination treatments were devised to use drugs that individually produced some level of anti-cancer activity. In selecting drugs for use in combinations, scientists try to take advantage of differing modes of anti-cancer activity while avoiding an increase in undesirable side effects. The current NCI studies have indicated that improvements in survival similar to those in Hodgkin's disease and childhood leukemia eventually may be possible in the treatment of breast cancer and cancer of the ovary.

Dr. DeVita, working with Robert C. Young, M.D., George P. Canellos, M.D., and others in the NCI Medicine Branch, treated 25 advanced breast

(more)

Drug Combinations (Cont'd)

cancer patients with a combination of four drugs: methotrexate, 5-fluorouracil, cyclophosphamide, and prednisone. Most of the patients had suffered a relapse of the disease after initial treatment by surgery, and the majority had also been treated previously with radiation, hormones, or removal of hormone-secreting glands.

The drugs produced at least a partial response in 17 (68 percent) of the patients, including a complete disappearance of cancer in seven (28 percent) of them. (A partial response is defined as at least a 50 percent decrease of measurable disease for more than two months.) The most favorable responses occurred in patients whose disease had spread to the lungs, soft tissue, or lymph nodes.

Breast cancer patients who responded to the drug combination have lived significantly longer than those who failed to respond. The eight (32 percent) nonresponders have had a median survival time of six months; that is, half of the group died within six months after treatment began. The median survival time of the responders has not been reached but will be longer than 15 months. Three of the seven patients who responded completely are no longer being treated and are still free of disease.

A larger study of the combined drug treatment for breast cancer has begun with 179 patients at hospitals in NCI's Eastern Cooperative Oncology Group. The overall response rate so far is comparable to the NCI results, Dr. DeVita said, but it is too soon to know what the rate of complete responses will be.

Most previous studies of single drugs in the treatment of advanced

(more)

Drug Combinations (Cont'd)

breast cancer have shown overall response rates (both partial and complete) of 15 to 30 percent, according to Dr. DeVita. Other studies with drug combinations have achieved overall response rates similar to the latest NCI results.

The NCI clinicians are also using a similar four-drug regimen to treat women with advanced cancer of the ovary. The so-called "HEXACAF" regimen is similar to the breast cancer treatment but includes hexamethylmelamine instead of prednisone. Twelve (40 percent) of the 30 patients treated so far have had a complete disappearance of all evidence of the disease. Data are not yet available on the total rate of partial and complete responses, or on the duration of responses among the 30 patients.

Dr. DeVita pointed out that single drugs have produced overall response rates of 40 to 60 percent in the treatment of advanced ovarian cancer, but complete response rates did not exceed 20 percent. Previous studies with drug combinations have not shown improved response rates in advanced cancer of the ovary.

#

GENETIC DISORDERS--There are more than one thousand genetic disorders that afflict man, including inborn errors of metabolism. The National Institutes of Health reports that 40 can now be detected before birth by tests of the amniotic fluid obtained by amniocentesis from the pregnant mother.

Research Advances

HIGH-DOSE RADIATION AND DRUGS
AID EWING'S SARCOMA PATIENTS

Children and young adults with early stages of a bone cancer called Ewing's sarcoma have a 50 percent chance of surviving at least five years if treated by a combination of high-dose radiation and drugs, National Cancer Institute (NCI) scientists report.

Thomas C. Pomeroy, M.D., and Ralph E. Johnson, M.D., explained projected survival data from their study of this rapidly fatal cancer at the NCI-sponsored Symposium on Combined Modality Therapy of Cancer in Denver on February 8, 1974. They included data on 66 consecutive patients treated for Ewing's sarcoma at the NIH Clinical Center during the past ten years. Forty-three of these patients were diagnosed with localized disease, and 23 had obvious metastasis, or spread of their disease.

The projected five-year survival rate for patients with localized disease in the NCI study is 52 percent. Short-term survival also is improving for patients whose cancer was widespread when diagnosed.

The success of the radiation plus drug combination treatment is evident when survival rates with the new treatment are contrasted with survival rates of ten years ago. In 1964, when the NCI study began, only one patient in ten with Ewing's sarcoma could expect to survive five years. The usual treatment for the disease at that time was either surgery or radiation alone.

The NCI treatment protocol combines irradiation of the primary cancer, drugs plus radiation treatment for possible brain metastasis, and inter-

(more)

Ewing's Sarcoma (Cont'd)

mittent administration of high doses of anti-cancer drugs. Fifteen of the 43 patients with localized disease were treated more than four years ago; seven of the 15 are alive and have been free of the disease for four to nine years. Increasing numbers are expected to reach this point in the coming years as combination treatments continue to improve.

Following irradiation of the primary cancer, the NCI scientists administer methotrexate through the spinal canal, and irradiate the brain to kill cancer cells which may have spread to those sites. No subsequent spread of cancer to the brain has been detected in 30 consecutive patients treated in this manner since 1969.

The scientists now administer four cycles of the anti-cancer drugs adriamycin, cytoxan, and vincristine to their patients. The entire treatment regimen rarely extends beyond six months, in contrast to other combination treatments for Ewing's sarcoma which may continue as long as two years. The incorporation of adriamycin in NCI's current drug combination, starting in 1971, appears to be producing a still further improvement in projected survival.

The NCI scientists admitted that their protocol, encouraging as it appears at present, would not be easy for physicians to use in general medical practice. They recommend instead that physicians refer their patients to major medical centers where combination treatments are under study. The scientists pointed out that as more patients are added to these studies, and comparisons of various treatment protocols become possible, further improvements in combination treatments will result.

Research Advances

DES In Utero...

STUDY ATTEMPTS TO DETERMINE RISK
FOR DEVELOPING VAGINAL CARCINOMA

On the basis of findings from a study of the children of mothers who received estrogen therapy during pregnancy, Mayo Clinic investigators estimate the incidence of vaginal or cervical cancer associated with in utero exposure to estrogens to be no greater than 4 per 1,000.

This finding is important in light of recent retrospective case-control and tumor registry reports which have produced a strong impression that such exposure is associated with vaginal and cervical adenocarcinoma in young women.

Because of such reports, investigators at the Mayo Clinic designed a prospective study of children born between 1943 and 1959 in hospitals affiliated with the Clinic. The objectives of the study were to determine the indications for the types and dosages of estrogens given to pregnant women during the years in question, the proportion of pregnant women treated and from that an estimate of the children exposed in utero, the risk that a young women will develop vaginal or cervical adenocarcinoma after exposure to DES in utero, and whether males exposed to DES in utero were also at increased risk of developing genitourinary cancer.

Among the 24,000 children born at the facilities during the period in question, the investigators identified 1,719 (818 females and 901 males) whose mothers had received the drug during pregnancy. Follow-up by physical examination or mailed questionnaire was completed up to 1970 or later in 99 percent of the cases.

(more)

Vaginal Carcinoma (Cont'd)

According to the findings, DES was the type of estrogen used in 93 percent of the cases and conjugated estrogens-equine in seven percent. Progesterone in some form was given additionally to 26 percent of the women.

Of the children, 57 percent were exposed to estrogen during the first trimester, and approximately one-third of these also were exposed to progestational drugs in the first trimester. In 67 percent of the cases, indications for estrogen treatment included symptoms of threatening abortion or previous history of miscarriage, stillbirth, or premature delivery.

The follow-up of the children ranged from 11 to 30 years, with the median age for each child being 22 years at the time of the report. The investigators found no cases of cancer of the vagina or cervix in any of the young women and no cases of genitourinary malignancy among the young men.

In the group of children, 126 were known to have died: 38 were still-born; 61 died during the first year (44 of complications of prematurity); and of the remaining 27 deaths, only two have been ascribed to malignancy. One was an eight-year-old girl with acute leukemia and the other, a 10-year-old boy with reticulum-cell sarcoma.

Among the remaining children, no increase of any kind of cancer--either in females or males--was discovered.

According to the investigators, the finding of no vaginal cancer in any of the females exposed to DES in utero can be interpreted in many ways:

1. there is no association;
2. an association exists but the risk is low;
3. an association exists but the outcome is affected by additional factors

(more)

Vaginal Carcinoma (Cont'd)

such as type of estrogen administered, dosage and time of treatment, use of progesterone or other drugs, or maternal factors.

However, the possibility of the reported association of DES and vaginal cancer being spurious seems unlikely to the investigators at this time. They explain that in the hypothesis of a causal relationship between DES treatment of the mothers and development of vaginal or cervical adenocarcinoma in the daughters, it is assumed that DES is carcinogenic, there has been transplacental transfer of DES, and that the effect of DES may not become manifest for many years. These assumptions, according to the Mayo investigators, are consistent with current theories of carcinogenesis and can be supported to some extent by experimental evidence.

Therefore, assuming a true association exists between in utero exposure to synthetic estrogens and clear-cell adenocarcinoma of the vagina and cervix in young women, the researchers attempted to find the risk of developing this type of cancer after exposure. No invasive vaginal or cervical cancer occurred in their study population, and from this they estimated that the risk of cancer to be less than 4 per 1,000 for the age limits of the study population. If the analysis is limited to those exposed to synthetic estrogens in the first trimester, the risk of developing the disease by age 13 is no greater than 7/1,000; by age 16, less than 8/1,000; by age 19, less than 9/1,000; and by age 22, less than 13/1,000.

The significance of forms of progesterone taken cannot be estimated at present.

The investigators recommend additional studies of unbiased cohorts,

(more)

Vaginal Carcinoma (Cont'd)

particularly since the clinical indications and dosage of estrogens used at the Mayo Clinic during this period were less than the amount recommended and may have differed from those in other parts of the country. Even though it cannot be assumed that other obstetric units followed the same pattern of drug usage as in the present study, the investigators hope that their report, together with those from other parts of the country, will provide reasonable estimates of the number of persons exposed prenatally to estrogens who may be at some special risk of developing vaginal cancer or possible other disorders.

Investigators Anne P. Lanier, M.D.; Kenneth L. Noller, M.D.; David G. Decker, M.D.; Lila R. Elveback, Ph.D.; and Leonard T. Kurland, M.D., reported their findings in the *Mayo Clinic Proceedings*, November 1973. Drs. Elveback and Kurland are grantees of the National Institute of General Medical Sciences. Dr. Decker is a grantee of the National Cancer Institute.

#

MACULAR DEGENERATION--Macular degeneration is irreversible and progressive damage to the macula portion of the retina resulting in a gradual loss of reading vision. The National Institutes of Health reports that this is a leading cause of blindness in the United States. Macular degeneration is usually associated with aging.

Photo Feature

ALASKA "WINTER WALK" PROGRAM
SIMULATES WORKING CONDITIONS

In a study conducted by scientists at the University of Alaska at Fairbanks, male volunteers participated in a 14 day, 12-hour per day, outdoor winter work regime simulating, as closely as possible, working conditions on the North Slope.



Participants in the "Winter Walk" program simulate prolonged North Slope work schedule by walking 12 hours daily for fourteen consecutive days. (NIH Photo #1206)

The program on the adjustments and capabilities of human subjects under arctic winter conditions was supported by the National Institute of General Medical Sciences.

The subjects walked at a rate of about 20 miles per day from 7 a.m. to 7 p.m., with temperatures ranging from -4°C to -44°C .

Each man tested received comprehensive medical and psychological examinations on the day preceeding the start of the work program. At scheduled intervals thereafter, all subjects were examined for changes in physical fitness, finger dexterity, and motor reflexes.

There were no dramatic changes in the ability of subjects to perform any of the psychomotor performance tests. As expected, subjects with cold hands took longer to accomplish the coordination tests (screwdriver and

(more)

Winter Walk (Cont'd)



A volunteer in the "Winter Walk" program takes screw tightening and pipe assembly tests to determine muscle coordination. (NIH Photos #1207, 1208)



pipe fitting tests), especially when temperatures ranged from -20°C to -44°C .

Under the established working regime, the physical condition of the subjects did not deteriorate--as in hot climates --but rather improved.

Participant takes blind stand test to evaluate neurophysiological functions associated with balance. (NIH Photo #1209)

#

NEWS FEATURE

Human Growth Hormone...

U.S. MEDICAL CENTERS
RECEIVE SCARCE HORMONE

Approximately 1,000 children nationally are receiving human growth hormone (HGH) through the National Pituitary Agency. The Agency, located at the University of Maryland and financed by the National Institute of Arthritis, Metabolism, and Digestive Diseases, distributes the scarce hormone to 52 U.S. medical centers.

At the University of Chicago's Silvain and Arma Wyler Children's Hospital, 12 children are under treatment in this particular "growth" program.

The children entering the program first undergo tests to determine if their abnormal lack of growth is due to growth hormone deficiency. The tests require hospitalization at the University's General Clinical Research Center for five days. (The Center is supported by NIH's Division of Research Resources.) The patients then obtain their initial growth hormone shots during a 20-day study of hormone action while at the Hospital. Subsequent shots can be administered by parents at home.

A key to identifying stunted children at an early age is the fact that they grow only about an inch a year, in comparison to normal children who grow about two to three inches a year. Ninety percent of abnormally short children in the Chicago program whose problem was caused by deficient HGH secretion have grown at an accelerated pace when given the hormone.

(more)

Hormone (Cont'd)

All of the nation's supply of HGH comes from human pituitaries (embalmed or nonembalmed) obtained by hospital pathologists during autopsies. The College of American Pathologists offers full cooperation and support to this program.

The hormone is extracted, put in small pharmaceutical bottles in powdered form, and then mixed with distilled water for injection. A process has been developed to synthesize a large molecule similar to HGH but only 10 percent as active as HGH. However, synthesis of the complete molecule for therapeutic use may take many more years of research.

Special tests to measure HGH in a child's blood plasma are necessary because HGH is secreted in episodes during the day and during certain phases of sleep and it is difficult to test for the hormone during these periods.

One of these tests, the insulin test, was first used to test for pituitary reserves of HGH in children in the mid-1960's. It discriminates between patients with normal pituitary function, whose HGH secretion increases in response to insulin-induced hypoglycemia and hypopituitary patients who do not respond to the test.

The levodopa (L-dopa) test is based on the fact that L-dopa stimulates the hypothalamus and causes the pituitary to secrete HGH. This test requires less close monitoring than the insulin test.

Both tests utilize the radioimmunoassay methods to detect tiny quantities of trace materials in biological fluids. In response to those tests, plasma concentrations of HGH rise above 10 nanograms per milliliter. (A nanogram is one billionth of one gram.) Only the radioimmunoassay tests can detect such small quantities.

Photo Feature

LEARNING DIFFICULTIES LINKED
WITH RESPONSE TO ENVIRONMENT

Most learning difficulties experienced by hyperkinetic children in classroom work may not be due to birth defects, but rather to an inherited response to an environmental or learning situation, according to psychologist Richard L. Sprott, Ph.D.



Dr. Richard L. Sprott examines one of his "students." (NIH Photo #1210)

Working with laboratory mice of specific strains, Dr. Sprott has found that by simply altering the environment, "slow-learning" mice can better their achievement record. Further, the performance of mice that have displayed a record of good learning behavior under normal conditions can also be reversed by making environmental changes.

Dr. Sprott and his staff have been studying the genetic analysis of learning behavior at the Jackson Laboratory in Bar Harbor, Maine, since 1965 with the help of General Research Support funds administered by the NIH Division of Research

(more)

Learning Difficulties (Cont'd)

Resources. He has observed more than 2,000 "students"--consisting of passive mice (strain C57/BL65) and aggressive mice (strain DBA/2J).

Armed with the fact that the passive mice typically do better at the task (avoidance of electric shock) than the aggressive mice, Dr. Sprott and associates conducted a complex series of trials covering 30 days for each of the "students." They introduced two variables for each of the tests: different age levels of mice were used, and footshock intensity was varied from mild to strong. These conditions introduced throughout the experiment altered the performance of the animals considerably.

Relating the significance of his study with mice to the problems of child behavior "definitely indicates the need for meaningful recognition of the fact that genetic differences are real and contribute to learning and performance," Dr. Sprott says.

In the case of the hyperkinetic child, Dr. Sprott maintains that the free school system would be of distinct advantage and quite possibly allow the child to excel. "The situation at a free school--where children are pretty much allowed to work at their pace--would allow a high activity level. High activity and much noise and distraction may not hamper the hyperkinetic child's progress as much as a passive child," he says.

Dr. Sprott believes that complex behaviors can be broken down into component parts for analysis. "Most behaviors, particularly those of any interest, are complex and consist of smaller units of behavior added together," the scientist points out. "Learning behavior, for example,

(more)

Learning Difficulties (Cont'd)

consists of motor skills like eye and hand coordination, brain capabilities, motivation to learn, attention state, and other factors all working in concert. An analysis of all of these factors at the same time is impossible, but it may be possible to analyze them one at a time."

Called a "single locus hypothesis," Dr. Sprott's findings about the effects of environmental variables on one type of learning performance may have direct application in human educational situations.

#

CRIB DEATH--Sudden infant death syndrome (SIDS) is the leading cause of death among U.S. infants between one month and one year of age, according to the National Institutes of Health.

DIGESTIVE DISEASES--Disorders of the gastrointestinal system, which include diverticulosis, peptic ulcer, and ulcerative colitis, are among the most common serious illnesses in this country, according to the National Institutes of Health.

HYPOGLYCEMIA--Most cases of hypoglycemia (low blood sugar) result from overproduction of insulin by the pancreas, and are manifested by symptoms similar to those which occur when a diabetic patient takes too much insulin, according to the National Institutes of Health.

Medical News Tip

COOLEY'S ANEMIA--Cooley's anemia (also known as Mediterranean anemia or thalassemia major) is the most common of the thalassemias, a group of genetically-determined blood disorders. The main biochemical defect in the diseases is the body's inability to produce red blood cells with a sufficient amount of hemoglobin. Normal red blood cells have a life span of three to four months, and as they die they are continuously replaced by new cells. In Cooley's anemia, the red blood cells cannot survive for more than a few weeks, resulting in anemia that appears shortly after birth and becomes progressively worse.

Both parents must carry and transmit the trait for Cooley's anemia for their child to develop the disease. Although individuals whose ancestors were natives of the countries surrounding the Mediterranean Sea, particularly Italy and Greece, are most likely to inherit Cooley's anemia, the gene defect has now been distributed through intermarriage to approximately 200,000 Americans of varied backgrounds.

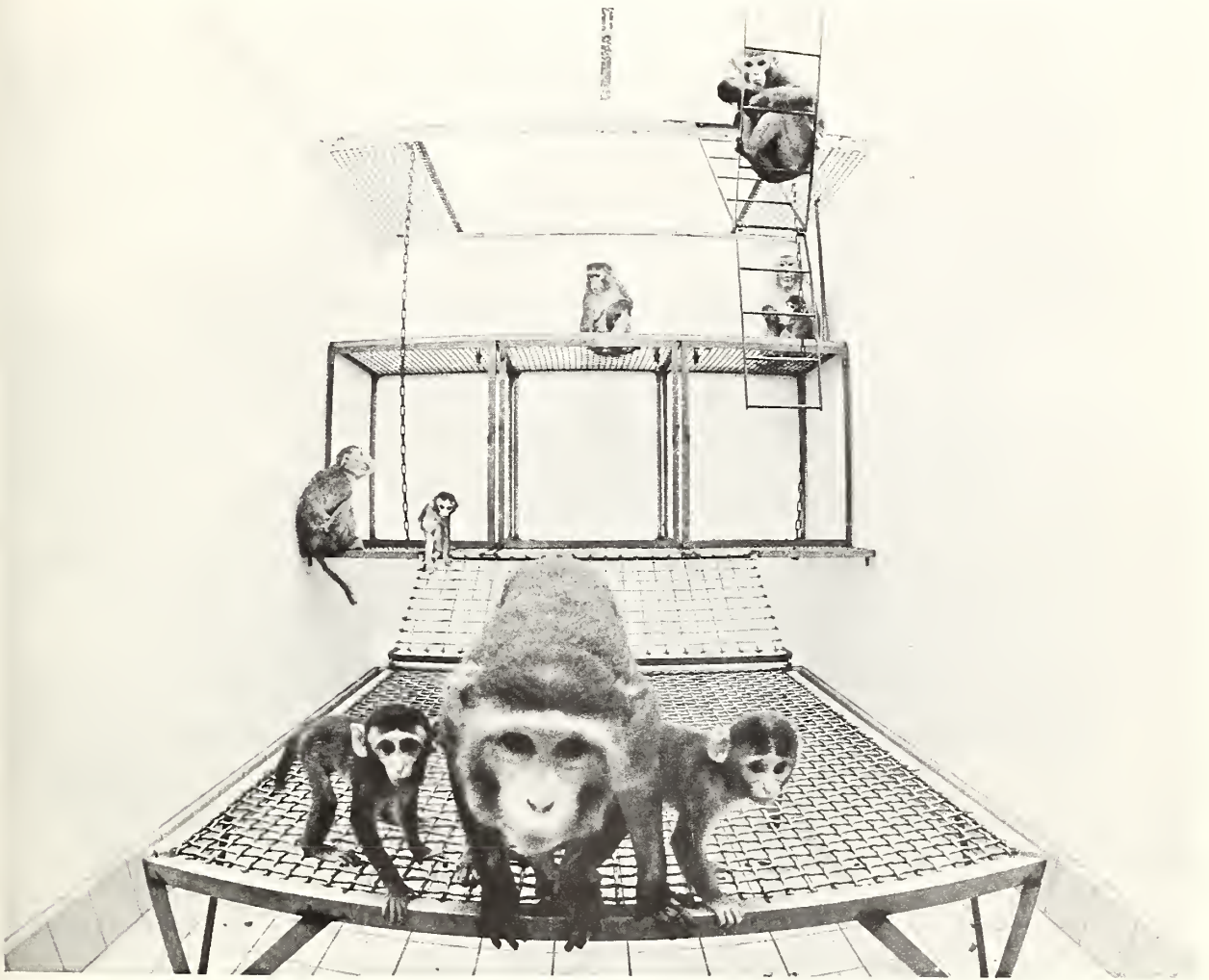
Individuals who inherit the hereditary defect from only one parent will develop a minor form of thalassemia which can either manifest itself as a mild form of anemia or may present no symptoms at all. Since this condition never worsens or converts to thalassemia major, individuals with thalassemia minor have a normal life span and normal health.

For additional information about Cooley's anemia, contact:

National Institute of Arthritis, Metabolism, and Digestive Diseases
NIH, Building 31, Room 9A-04
Bethesda, Maryland 20014
Phone: (301) 496-3583

Capsules

RESEARCH ILLUSTRATED



A study on sex differences in infant behavior during the first year of life is being conducted with Rhesus monkeys at the Wisconsin Regional Primate Research Center in Madison. Two of the infants pictured here are female, two are male. Derman (infant at lower right) is a "pseudohermaphrodite." She is genetically a female, but has many morphological and behavioral characteristics of a male because her mother (center) was treated with male hormones before Derman was born.

Pediatric biochemistry and mental retardation research, conducted in the Center's metabolic nursery, have yielded important data related to the study of inborn errors of man. The Center is supported by NIH's Division of Research Resources. (NIH Photo #1211)

New Publication:Hepatitis

Each year thousands of Americans are afflicted by the debilitating combination of fever, malaise, nausea, and jaundice that characterizes hepatitis. This sometimes fatal illness is one of the major unsolved infectious disease problems of man.

Viral hepatitis is a worldwide problem. In the United States alone in a recent year, more than 60,000 cases of the disease were reported. However, the true incidence is believed to be much higher--perhaps ten times the reported figure. Due to difficulty in diagnosing hepatitis and the failure of many patients to seek medical care, not all cases are recorded by public health authorities.

Hepatitis is, therefore, the target of intensive research supported by the National Institute of Allergy and Infectious Diseases (NIAID). As a result, prevention of hepatitis is more of a possibility today than ever before.

A new publication, *Hepatitis*, released by NIAID deals with the causes, types, symptoms, treatment, and prevention of this dread disease.

Science writers can obtain a free copy of this publication from:

NIAID
National Institutes of Health
Building 31, Room 7A-32
Bethesda, MD 20014
Phone: (301) 496-5717

News Releases Issued

SICKLE CELL--Earlier publicized claims that urea infusions might be of special value in the treatment of sickle cell crises have not been borne out by the results of a two-year clinical trial at six institutions. The trial which evaluated and compared three modes of therapy, was supported by contracts from the Sickle Cell Disease Branch of the National Heart and Lung Institute. The results of the study indicated that urea offered no advantages over therapeutic measures to correct dehydration or excess blood acidity. Except for a few instances of headache and vein irritation, urea caused no apparent significant side effects in this trial. Its use, however, required meticulous technique and careful attention to the patient's fluid and blood electrolyte balance. None of the regimens proved satisfactory for controlling the painful, frequently disabling crises for the 50,000 Americans who are affected by sickle cell anemia.

#

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March 10, 1974



See page 7

Page

RESEARCH ADVANCES:

Gray Collie Receives Bone Marrow Transplant.....	1
Adults Profoundly Affect Infant Personality Development.....	3
Tooth Surface Reactions Suggest New Enamel Etchant.....	5

NEWS & PHOTO FEATURES:

"Bank" Stores Cells For Genetics Studies.....	7
---	---

MEDICAL NEWS TIP:

Diverticulosis and Diverticulitis.....	10
--	----

NEW PUBLICATION:

<i>Flu</i>	11
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Research Advances

Inherited Blood Disease...

GRAY COLLIE RECEIVES
BONE MARROW TRANSPLANT

A gray collie dog suffering from cyclic neutropenia has been cured of the disease by a transplant of normal bone marrow cells. Because the human and canine forms of this hereditary blood disease are similar, scientists believe that the human disease may also be cured by marrow transplantation.

Although cyclic neutropenia is a rare disease in humans, it is of interest to researchers who believe that an understanding of it will lead to a basic understanding of leukemia and aplastic anemia. David C. Dale, M.D., and Sheldon M. Wolff, M.D., of the National Institute of Allergy and Infectious Diseases, have been studying the disorder in gray collies for the past five years.

Cyclic neutropenia is characterized by periodic and precipitous drops in the level of circulating white blood cells. Fever and painful ulcers in the mouth and elsewhere on the body are also common symptoms of the disease.

In humans, the decline in blood cell levels occurs every 21 days; in gray collies, every 12 days. During this period, both humans and collies are very susceptible to serious infections. In fact, gray collies rarely live longer than a year, with most of the animals dying from overwhelming infection in their first few weeks of life.

To determine whether the disease is caused by a defect in the bone marrow cells which causes the dog to stop producing white blood cells, Dr. Dale and Robert G. Graw, Jr., M.D., of the National Cancer Institute, trans-

(more)

Gray Collie (Cont'd)

planted bone marrow cells from a normal 10-month-old male collie with normal coat color and normal serial blood cell counts to an unrelated one-year-old female sable-gray collie with well-documented cyclic neutropenia. The investigators report that after transplantation, there were no further periods of neutropenia. Also, the animal showed a noticeable decrease in the chronic inflammation about the eyes, gum margins, and other tissues.

From days 28 to 35 after transplantation, the dog developed mild graft-versus-host disease indicated by mild conjunctivitis, rhinorrhea, and intermittent low grade fever. However, at 80 days after transplant, the dog was well, showing a normal white cell production and no signs of chronic graft-versus-host disease.

The dog eventually died of causes apparently unrelated to the transplant or cyclic neutropenia.

Although the human disease may also be cured by marrow transplantation, at present the technique is considered applicable only to treatment of life-threatening human disease, such as leukemia or aplastic anemia.

Drs. Dale and Graw published their findings in *Science*, January 11, 1974.

#

CANCER--Surgery, radiation, and drug treatment--singly, but more often in combinations--are the principal focus of cancer treatment research, according to the National Institutes of Health.

Research Advances

ADULTS PROFOUNDLY AFFECT
INFANT PERSONALITY DEVELOPMENT

When a working mother leaves her baby in care of a babysitter, will the child's personality be affected?

Research on young infants indicates that personality and mental development at six months of age are independent of whether babies are cared for by their own mothers full-time, or by a combination of the mother and part-time caretakers while the mother works outside the home.

This research assessed individually many of the factors which affect personality development in babies. Leon J. Yarrow, Ph.D., and associates at the Social and Behavioral Sciences Branch of the National Institute of Child Health and Human Development, designed a method for the assessment of these factors.

On all of the 11 measures of stimulation which were examined, mothers scored higher than substitutes. Mothers were more likely to play to express positive feelings toward the infants, to place toys within the baby's reach, to provide a wide selection of playthings, and to interact with the baby in a variety of ways.

However, infants cared for by mothers did not differ at six months of age in mental and personality developments from babies with part-time substitute mothers.

The importance of the father, at least to sons, emerged when Dr. Yarrow and associates applied the method to another study. Female infants, five to six months old, were not measurably affected by a lack of father interaction. In male infants, however, important measures of mental, social,

(more)

Infant Personality (Cont'd)

and motivational development were related to how much interaction they had with their fathers. Male babies with more interaction were, at six months of age, more alert, responsive, and interested in their environment.

Dr. Yarrow speculates that the father may function to complement stimulation by the mother and to introduce novelty into the infant's daily routine. Why only male infants seemed affected by the absence of the father is puzzling.

Although the study did not precisely explain the nature of the father's effect, it does indicate that the mother is not the sole major influence on the young infant.

#

CORNEAL DISEASES--One of the most difficult corneal diseases to treat is that caused by the herpes simplex virus. Although the virus infection may be temporarily relieved, it often recurs, according to the National Institutes of Health.

CORONARY BY-PASS--An estimated 20-25,000 patients undergo the coronary artery bypass operation each year, according to the National Institutes of Health.

RESPIRATORY DISTRESS--Respiratory distress syndrome is the leading cause of death among the newborn. Certain pediatric lung diseases may also be the forerunners of chronic lung disease in adult life, according to the National Institutes of Health.

IN THE LITERATURE:

Journal of Dental Research, September-October, 1973

TOOTH SURFACE REACTIONS SUGGEST NEW ENAMEL ETCHANT--Basic research into reactions occurring on tooth surfaces suggests to dental scientists that a new, modified etchant may be safer than, and just as effective as, the conventional 50 percent phosphoric acid solution now used to treat enamel before applying sealants to chewing surfaces of teeth.

The investigators, in work supported by the National Institute of Dental Research, report that a solution of not less than 27 percent phosphoric acid to which some calcium phosphate has been added is less acid and removes less tooth mineral. They suggest that 35 percent phosphoric acid and 2.7 percent calcium hydroxide might be a better solution.

Laurence C. Chow, Ph.D., and Walter E. Brown, Ph.D., of the American Dental Association Research Unit at the National Bureau of Standards, Gaithersburg, Maryland, found a variety of reactions which occur on the surface of teeth as the strength of phosphoric acid is changed from zero to 100 percent. Previous solutions were developed on a trial and error basis; this work establishes a scientific rationale for improvements.

Very concentrated acid dissolves less enamel mineral than does a more dilute acid because when the concentrated acid reacts with the mineral it quickly forms a layer of crystals (monocalcium phosphate monohydrate, $\text{Ca}(\text{H}_2\text{PO}_4)_2 \cdot \text{H}_2\text{O}$). These crystals provide a protective coating over the surface. However, the crystals are readily soluble in water. Therefore, when a tooth is rinsed after acid pretreatment, the crystals wash away leaving a clean surface with microscopic openings in the enamel. These pores improve the attachment of the sealant.

(more)

Enamel Etchant (Cont'd)

When the solution contains less than 27 percent acid, another precipitate (dicalcium phosphate dihydrate, $\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$) can form which is not very soluble and therefore cannot be rinsed away easily. In this case, the openings in the enamel would be covered and a sealant could not attach very well.

The solution Dr. Brown's group suggests should have the advantages of being less acid and removing less mineral because it already has calcium phosphate added, without the disadvantage of forming insoluble crystals to clog the openings necessary for sealant attachment, but it must be tested clinically before conclusions can be drawn.

#

DETECTION--Early detection, while the cancer is localized or limited to the organ of origin, offers the best opportunity for control in most forms of cancer, according to the National Institutes of Health.

CATARACT--A new hypothesis of senile cataract formation has led to the induction and subsequent reversal of a cataract in a test tube culture which is believed to parallel the condition which occurs in elderly patients, according to the National Institutes of Health.

Photo Feature

**"BANK" STORES CELLS
FOR GENETICS STUDIES**

The Institute for Medical Research operates a repository of human mutant and normal cell cultures for genetic and biochemical studies. The development of this extensive cell bank is supported by a National Institute of General Medical Sciences (NIGMS) contract.

Such NIGMS-supported genetic diseases research is now beginning to provide a firm basis for genetic counseling, early diagnosis, prevention, prenatal detection, and, in a few cases, treatment.

The repository, which is located in Camden, New Jersey, contains viable cells in low passage (cells that will divide many more times) representing hereditary diseases and the carrier state. Also available are cells with useful phenotypic gene markers, chromosomal abnormalities, and normal controls.

The cells are distributed to professionals who are associated with recognized research, medical, educational, or industrial organizations engaged in health-related research or in the delivery of health care.

The central repository gives such investigators the opportunity to identify and compare cells, increases the availability of rare cells lines, and eliminates the need for investigators in different labs to develop and maintain numerous cell lines.

Lewis L. Coriell, M.D., Ph.D., director of the Institute, is principal investigator of the cell repository. Arthur E. Greene, D.Sc., heads the Cell Biology Department where biopsies are established in culture and cells are grown and preserved. Warren W. Nichols, M.D., Ph.D., heads the Cytogenetics Department which provides cytogenetic characterizations of the cell lines for scientists.

(more)

Cell Bank (Cont'd)

A skin biopsy, along with patient data, is sent to the Institute for Medical Research where it will be cultured to establish a cell line available to any scientist conducting research on the patient's genetic disease. From the moment the flask containing the biopsy is first opened until the cultured cells are inoculated into ampules for sealing, all operations are performed in hoods, tents, and laminar flow rooms to eliminate all possibility of contamination by airborne microorganisms (right). After washing the biopsy in culture media, the technician cuts it into minute pieces to accelerate cell proliferation, places the pieces in a culture flask, and adds media (below). (NIH Photos #1212, 1213)

(more)



Cell Bank (Cont'd)

After three to four weeks in an incubator room (right), the surface of the flask around each piece of tissue is covered with cells which are then transferred to additional flasks to continue proliferation. When 12 to 25 flasks have been accumulated, all the cells can be harvested in ampules--one-half million cells per ampule (below, right)--and prepared for storage in liquid nitrogen at 316 degrees Fahrenheit below zero where they retain viability indefinitely. The ampules are heat-sealed and placed in indexed compartments in the liquid nitrogen storage tank until required for research (below, left).

(NIH Photos #1214, 1215, 1216)

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Medical News Tip

DIVERTICULOSIS AND DIVERTICULITIS--Diverticulosis is a condition of the digestive tract characterized by tiny mucosal sacs (diverticula) which protrude through the muscular wall of the large intestine. If these sacs become infected, the condition is known as diverticulitis, or inflammation of the diverticula.

More than 30 percent of persons over 45 years of age and over 80 percent of those over 60 have diverticulosis, and more than 25 percent of these develop the infected form, diverticulitis. The condition is found more often in women than in men.

The exact cause of diverticulosis is as yet unknown. In all cases studied, however, a thickening of the muscular wall of the intestine was found. Studies have also demonstrated that the combined pressure of food and gas on soft spots, usually near blood vessels in the abnormally thickened intestinal wall, may precipitate development of sacs. Chronic constipation and the ensuing use of high-powered cathartics increase the pressure.

Infection results when bacteria which normally inhabit the digestive system act on tiny particles of undigested material such as seeds or by small hard feces retained too long in the lower intestine, producing substances which are irritating to the lining of the sacs.

For additional information about diverticulosis and diverticulitis, contact:

National Institute of Arthritis, Metabolism, and Digestive Diseases
NIH, Building 31, Room 9A-04
Bethesda, Maryland 20014
Phone: (301) 496-3583

NEWS & FEATURES From NIH

March 10, 1974

New Publication:*Flu*

Flu, or influenza, is an acute respiratory illness with symptoms including fever, cough, sore throat, a "runny" nose, and general muscular aches.

Most patients recover completely within a week although many continue to feel unusually tired for some time. In the aged or the chronically ill, however, flu is a life-threatening illness. Together with pneumonia, it is the fifth leading cause of death in the United States.

Outbreaks of flu usually occur abruptly. This virus-caused disease spreads through communities, peaking in about three weeks and subsiding after another three or four weeks. Twenty to 50 percent of susceptible people may be affected, with the highest incidence in children, ages five to 14.

A new publication, *Flu*, released by the National Institute of Allergy and Infectious Diseases (NIAID) explains current vaccines for, treatment of, and research on influenza viruses.

Science writers can obtain a free copy of this publication from:

NIAID
National Institutes of Health
Building 31, Room 7A-32
Bethesda, MD 20014
Phone: (301) 496-5717

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See page 10

	<u>Page</u>
RESEARCH ADVANCES:	
Human Mycoplasmas Cause Bladder Stones.....	1
Bone Marrow Recipients Vary in Immunologic Recovery.....	3
Drug Helps Explain Asthma Mechanisms.....	5
NEWS & PHOTO FEATURES:	
NLM Exhibit Explores Witchcraft and Medicine.....	8
Framingham Eye Study To Determine Risk Factors.....	10
NIEHS Investigates Microwave Radiation.....	11
MEDICAL NEWS TIP:	
Hypoglycemia.....	12
NEW PUBLICATION:	
<i>Tetanus</i>	13

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Research Advances

In Experimental Animals...

HUMAN MYCOPLASMAS
CAUSE BLADDER STONES

A clue to the formation of urinary tract stones in humans may have been provided by the recently reported discovery that organisms known as T mycoplasmas can produce bladder stones in rats.

Mycoplasmas are the smallest free-living organisms known, being intermediate in size between viruses and bacteria. They are found in all animal life and in plants. However, with the exception of *Mycoplasma pneumoniae* (which causes an acute respiratory disease), these agents have not been proved to cause human illness.

The strain of T (for tiny) mycoplasmas used in these experiments was originally isolated from the urethra of a patient with non-gonococcal urethritis. Arthur M. Friedlander, M.D., and Abraham I. Braude, M.D., National Institute of Allergy and Infectious Diseases grantees at the University of California Medical School, San Diego, cultured the strain and then injected the organisms into the bladder or kidneys of Sprague-Dawley laboratory rats.

Six weeks later, the investigators found that bladder stones had developed in 78 percent of the male rats. However, no stones developed in female rats or in animals that had been injected with culture medium alone. (This sex difference has been reported previously in experiments involving stone formation.) Most rats with stones had thickened bladders and dilated ureters.

(more)

Mycoplasmas (Cont'd)

T mycoplasmas could be recovered from urine and kidney cultures of all animals injected with the organisms, whether or not they developed stones. No T mycoplasmas were found in animals which had not been inoculated.

Another mycoplasma species--*Mycoplasma hominis*--was also examined for stone-forming ability but with negative results. On the basis of this, the scientists established that stone formation is not a general property of mycoplasma species.

Since T mycoplasmas are known to inhabit the urinary tracts of a large percentage of men and women, to have a capacity for attaching to mammalian cells, and to aggregate mucoprotein (the principal component of stones), the investigators suggest that these organisms may serve as a nucleus and part of the organic matrix of human urinary tract stones.

The investigators reported this work in the January 4 issue of *Nature*.

#

HIGH BLOOD PRESSURE--May 1974 is National High Blood Pressure Month. According to the National Institutes of Health, high blood pressure can and must be controlled through continuing treatment by a qualified physician.

BREAST CANCER--The National Institutes of Health wants to make breast cancer screening more widely available throughout the country. In a joint program with the American Cancer Society, several breast cancer detection clinics are open where women can receive thorough examinations without charge.

Research Advances

BONE MARROW RECIPIENTS VARY
IN IMMUNOLOGIC RECOVERY

Investigators at the University of Washington report a significant difference in the immunologic recovery of patients receiving bone marrow transplants from twin and non-twin donors.

The scientists studied 13 leukemia or aplastic anemia patients receiving bone marrow transplants as treatment for their disease. Three of the patients were fortunate enough to have an identical twin who could be used as a marrow donor. Two of these patients received additional transfusions of donor white blood cells three times a week for four to six weeks after transplantation. In these two, immunologic recovery, indicated by the ability to make antibody and respond to skin test antigens, was particularly good. Although the third patient's recovery was not as complete, none of these recipients of twin marrow experienced serious infections following transplantation.

In contrast, immunologic recovery in the 10 patients who received marrow transplants from sibling (but non-twin) donors was slower and far less complete. Although "matched" for HL-A antigens (substances on white cells which determine tissue compatibility), the graft in one patient actually caused graft-versus-host disease which was brought under control by drugs. All patients had infections, some of which were serious. Even after one to two years, antibody production was inadequate. Reactions to skin test antigens were varied and, in some cases, lacking.

The investigators recently studied 50 dogs which, like the leukemia and anemia patients, had received non-twin marrow transplants after their own

(more)

Bone Marrow (Cont'd)

marrow had been destroyed by radiation, cytotoxic drugs, or a combination of the two. These animals, studied for immunological reactivity 20 days to eight years after grafting, did remarkably well. Although prone to infection during the first three months, the animals were able to live in an unprotected environment without apparent undue susceptibility to infections.

The investigators suggest that the much slower recovery of immunological functions seen in human recipients of non-twin marrow may be due to the fact that they received relatively smaller amounts of marrow than did the canine subjects.

The long-term immunologic deficiency observed in patients receiving non-twin marrow emphasizes the necessity for protection against infection and for early detection and prompt treatment of infection when it does occur. The investigators suggest that some of the deficiency might be overcome by administration of additional donor lymphoid cells to recipients but at the risk of increased graft-versus-host disease. Other areas which the scientists plan to explore include the use of transfer factor, which achieves specific immunity, and the stimulation of nonspecific immunity.

L. Fass, Hans D. Ochs, M.D.; E. Donnall Thomas, M.D.; Eric M. Mickelson; Rainer F. Storb, M.D.; and Alexander Fefer, M.D., reported their work in the December 1973 issue of *Transplantation*. This research was supported by the National Institute of Allergy and Infectious Diseases and the National Cancer Institute.

IN THE LITERATURE:

Journal of Allergy and Clinical Immunology, September 1973

DRUG HELPS EXPLAIN ASTHMA MECHANISMS--Scientists have found evidence that the drug phentolamine may be potentially beneficial in treating some asthma patients. In addition to leading to better therapy for some forms of asthma, their findings may help unravel the complex mechanisms of the disease.

Elliott Middleton, Jr., M.D., Ronald G. Coffey, Ph.D., and their associates Patricia J. Logsdon and Diane V. Carnright carried out the research at the Children's Asthma Research Institute and Hospital (CARIH) in Denver. CARIH is one of 17 Asthma and Allergic Disease Centers supported by the National Institute of Allergy and Infectious Diseases.

Phentolamine is an "alpha adrenergic blocking agent"; that is, it interferes with the response of the alpha adrenergic receptors. Alpha and beta adrenergic receptors are sites on cells, including those of the bronchial tissue. When stimulated by certain chemicals, alpha receptors lead to contraction of smooth muscle and decreased levels of adenylate cyclase, an enzyme responsible for the synthesis of cyclic AMP. Cyclic AMP is a substance that controls many cellular functions of the body and decreased levels of it lead to increased secretion of slow-reacting-substance of anaphylaxis (SRS-A) and histamine. These are chemical mediators responsible for many asthmatic symptoms. One theory holds that some forms of asthma are caused by "overreactive" alpha adrenergic receptors, resulting in the release of histamine and SRS-A.

Stimulation of beta receptors, on the other hand, leads to relaxation of smooth muscle, increased levels of adenylate cyclase and cyclic AMP, and decreased levels of SRS-A and histamine. Another theory holds that some

(more)

Asthma (Cont'd)

forms of asthma are caused by a blockade at the beta adrenergic receptors, resulting in decreased levels of cyclic AMP and increased levels of histamine and SRS-A.

Scientists have been searching, therefore, for drugs to treat asthma that will act by selectively blocking overreactive alpha receptors or by overcoming the blockade at beta receptors.

The CARIH investigators studied the effects of phentolamine on the activity of adenylate cyclase and cyclic AMP, because the levels of these two substances serve as a marker of SRS-A and histamine levels. They also studied the effect of phentolamine on the stimulation of cyclic AMP by isoproterenol, a drug long used in treatment of asthma. Isoproterenol is thought to act by overcoming the beta adrenergic blockade. The studies were done in white blood cells from asthmatic and nonasthmatic donors.

Drs. Coffey and Middleton found that phentolamine increased cyclic AMP formation in white blood cells from asthmatic children only 11.4 percent, whereas cyclic AMP in white blood cells from nonasthmatic children was stimulated 30.7 percent and from adults, 42.7 percent. This implies that phentolamine would exert therapeutic effects in asthma treatment by blocking alpha receptors. However, they also discovered that stimulation of cyclic AMP by phentolamine can be blocked by propranolol, a chemical that blocks beta receptors. This implies that phentolamine may also act by unblocking beta receptors, or that phentolamine exerts a dual action.

This implication is supported by additional experiments. The investigators found that the effect of the combination of phentolamine and isopro-

(more)

Asthma (Cont'd)

terenol on cyclic AMP activity in white blood cells was additive in some cases and synergistic in others. Phentolamine plus isoproterenol had an additive effect on cyclic AMP formation in white blood cells of nonasthmatic children. However, the combination of the two drugs produced a synergistic effect in cells of asthmatic children. Apparently, phentolamine permitted an enhanced stimulation of cyclic AMP by isoproterenol in white blood cells of asthmatics so that the isoproterenol effect reached the range seen with nonasthmatics.

The investigators suggest that the additive effect could be caused by phentolamine and isoproterenol acting independently to overcome the beta adrenergic receptor blockade. The synergistic effect could be due to the alpha receptor blockade by phentolamine, making available more isoproterenol to the beta receptor.

Although the data do not conclusively prove the precise mechanism of phentolamine, it appears that overreactive alpha receptors play an important role in the basic mechanism of asthma. The scientists recommend further studies of the potential therapeutic effects of alpha blocking agents.

#

HYPERTENSION--Twenty-three million Americans have high blood pressure and half of these are not aware they have the disease. Left uncontrolled, high blood pressure leads to heart failure, stroke, and kidney disease, according to the National Institutes of Health.

Photo Feature

NLM EXHIBIT EXPLORES
WITCHCRAFT AND MEDICINE

"Witchcraft and Medicine," the current exhibit at the National Library of Medicine (NLM), includes actual torturing devices used by witch-hunters in England during the 17th century, as well as books and reproductions dealing with exorcism and witchcraft trials. Samples of herbs used for inducing altered mental states in the "witches" before their sabbat ceremonies also will be on display.

The exhibit focuses on the attitudes of physicians, their examinations and diagnosis of "possessed" persons and "witches," their growing skepticism about the validity of practices established by the witch-hunters, and their efforts to transfer most of the suspects from the sphere of theology and criminal law to that of medicine.

The display covers the period between 1484, when Pope Innocent VIII issued a bull against witchcraft in Germany, which was interpreted as a general mandate for witch hunting; and 1793, when the last witch burning took place in Poland.

Johann Weyer (ca. 1515-1588), top photo, a pupil of Erasmus and physician to the Duke of Cleves, asserted that "demoniacs" were actually suffering from hysteria and hypochondriasis. He did believe, however, in the existence of witches, but considered them rare. Paracelsus (1493-1541), a physician, alchemist, and author, attributed witchcraft to mental disorders and stated that "mental diseases have nothing to do with evil spirits or devils...one should not study how to exorcise the devil, but how to cure the insane." (NIH Photos #1217, #1218)



(more)

Witchcraft (Cont'd)



In the woodcut from Pierre Boaistuau, *Histoires prodigieuses et memorables...*, Paris, 1598 (above), a priest (or bishop) exorcises a demon from a possessed woman (NIH Photo #1219). A meeting of witches is shown in the photo at right. The witch in the center of the circle inscribes cabbalistic signs within its perimeter. It was believed by witches that anyone who entered into communication with demons must be enclosed within the magic circle or suffer death.

Engraving by Diederich Lemicus from Nicolas Remi. *Demonolatria...*, Hamburg, Frankfurt, and Leipzig, 1693. (NIH Photo #1220). A wood engraving from Joost Damhouder, *Enchiridion...*, Rotterdam, 1554, (near right), shows the stretching of the accused on a rack or ladder, a method of torture used in France and Germany. (NIH Photo #1221).



The exhibit will be on display through July 19, 1974.

Photo Feature

FRAMINGHAM EYE STUDY
TO DETERMINE RISK FACTORS

The Framingham Eye Study is the first large-scale epidemiological investigation attempting to identify risk factors associated with the four leading causes of blindness and visual disability in this country: cataract, diabetic retinopathy, glaucoma, and macular degeneration.

Supported by a contract from the National Eye Institute to the Department of Ophthalmology of the Boston University School of Medicine, the Study involves the same population that participated for over twenty years in the Framingham Heart Study conducted by the National Heart and Lung Institute.

In the Eye Study, maximum participation is considered essential. Because the investigation is designed to study a strictly-defined population, it is important that as many eligible participants as possible be examined in order to obtain information that reflects the status of the entire group. For this reason, efforts are being made to educate the community and explain the value of the epidemiological research.

NOTE TO SCIENCE WRITERS: NEWS & FEATURES From NIH will include a special supplement on the Framingham Eye Study in a future issue.

#

Louis Ablondi (left) has been blind in one eye for 10 years. During an Eye Study examination, the beginning of a detached retina was discovered in his good eye. Surgery was performed and vision was restored in the eye within 24 hours. (NIH Photo #1222)

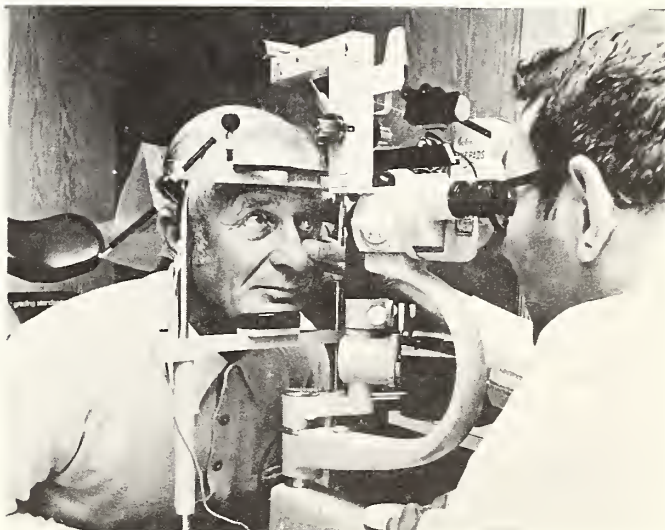
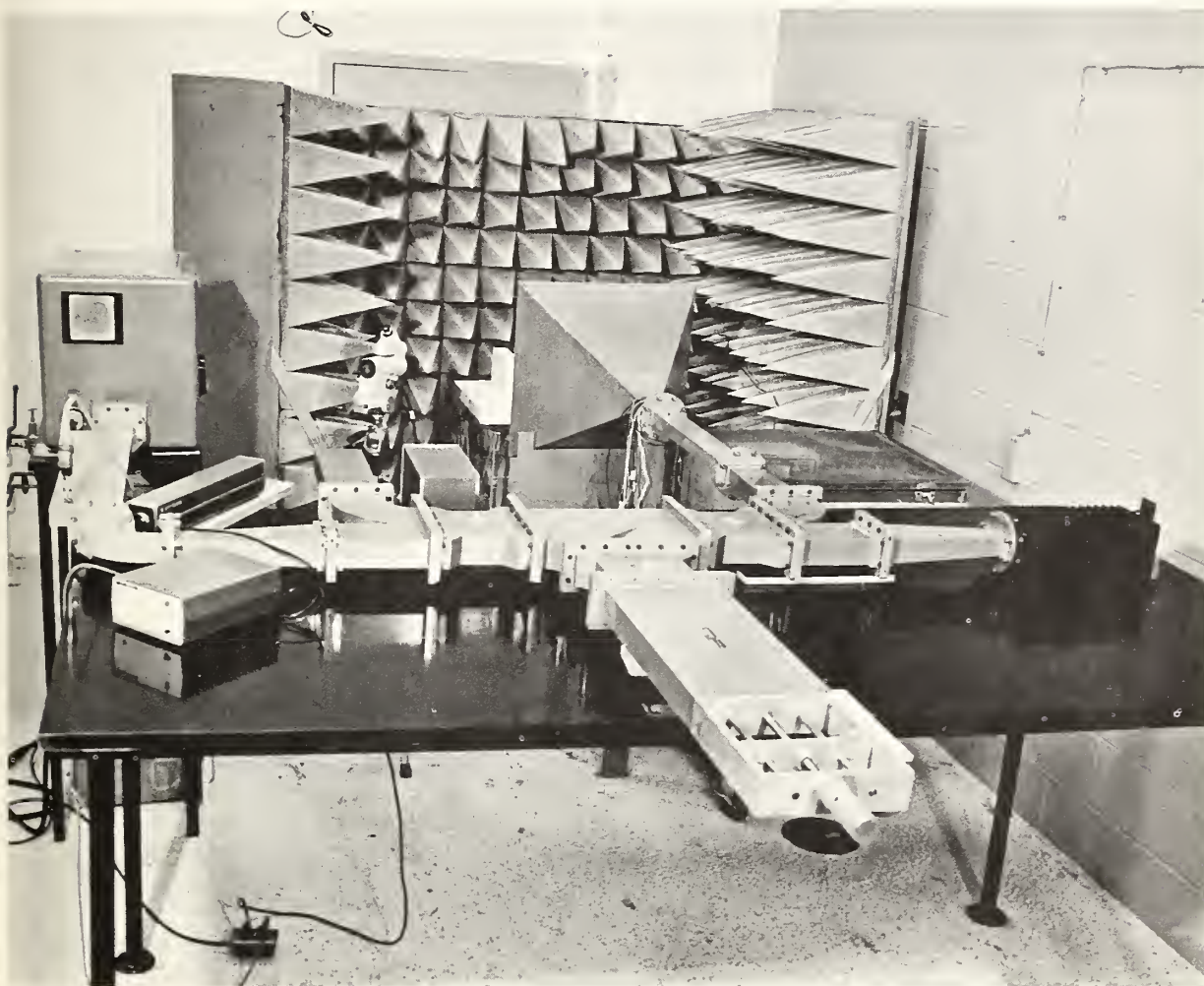


Photo Feature

NIEHS INVESTIGATES
MICROWAVE RADIATION

National Institute of Environmental Health Sciences researchers have developed exposure facilities and dosimetry techniques to study the biological effects of microwave radiation. The photo above illustrates a microwave exposure system where experimental models are exposed to defined levels of microwave radiation. (NIH Photo #1223)

Medical News Tip

HYPOGLYCEMIA--Hypoglycemia, a lower than normal level of sugar (glucose) in the blood, usually occurs several hours after eating and is characterized by sweating, trembling, palpitation, hunger, weakness, and lightheadedness. These symptoms may vary in duration and often disappear rapidly after eating a snack, a sweet, or drinking a glass of milk.

If the condition is not relieved, a further lowering of the blood sugar level may occur, leading to headache, irritability, and loss of mental acuteness. A few rare, severe, uncontrolled cases of "low blood sugar" may progress to visual and speech disturbances, convulsions, coma, and death.

Blood sugar levels are regulated by many factors, including the amount of carbohydrates in the diet (which are converted to sugar by digestion) and the action of the hormone insulin produced by the pancreas. Insulin acts to facilitate the entry of glucose into the cells of the body, thus providing much of the energy required for normal body functions. The brain, in particular, requires a constant supply of sugar from the blood for its normal activity.

Most cases of hypoglycemia result from overproduction of insulin by the pancreas, with symptoms similar to those which occur when a diabetic patient takes too much insulin or an excess of anti-diabetic pills.

For additional information about hypoglycemia, contact: National Institute of Arthritis, Metabolism, and Digestive Diseases, NIH, Building 31, Room 9A-04, Bethesda, Maryland 20014, Phone: (301) 496-3583.

New Publication:*Tetanus*

The National Institute of Allergy and Infectious Diseases (NIAID) has released a new publication, *Tetanus*, giving information about this ancient dread disease.

Tetanus, often called "lockjaw," develops as the result of a wound, usually a puncture or laceration. However, even a superficial scratch is susceptible to infection by tetanus bacteria. When tetanus infection does occur, it is highly lethal because of the toxin (poison) produced by the organism.

Although these bacteria produce one of the most deadly poisons known, a tetanus immunization injection given every ten years is one of the simplest, safest, and least expensive lifesaving procedures developed by modern medicine.

The initial symptoms of tetanus infection are likely to be restlessness, irritability, and muscular stiffness in the jaw, neck, or limbs as the toxin reaches the central nervous system. Later, painful convulsions begin to sweep over the victim's body. In spite of treatment, the convulsions may increase until the patient dies of asphyxiation, heart failure, or simple exhaustion.

Since no known drugs can block the effects of the toxin once they have begun, preventive measures should be instituted at once with any wound prone to tetanus. A physician usually recommends tetanus immune globulin or tetanus antitoxin along with an immunization injection.

Science writers can obtain a free copy of this publication from:

NIAID
National Institutes of Health
Bldg. 31, Room 7A-32
Bethesda, MD 20014
Phone: (301) 496-5717

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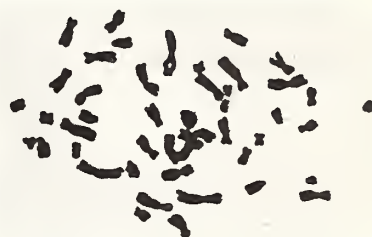
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See page 9

Page

RESEARCH ADVANCES:

Combinations of Anti-Cancer Drugs Treat Advanced Breast Cancer....	1
Male Contraceptive Drug Shows Promising Results.....	4
Hair Spray Exposure May Present Hazard.....	6

NEWS & PHOTO FEATURES:

Computer System Speeds Karyotype Preparation.....	9
Psoriasis Day Care Centers Eliminate Hospital Stay.....	11
Normal Volunteer Patients Participate in CC Studies.....	13

MEDICAL NEWS TIP:

Missing Enzymes.....	14
----------------------	----

NEWS RELEASES ISSUED:

MRFIT.....	15
------------	----

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Research Advances

Additional Studies...

COMBINATIONS OF ANTI-CANCER DRUGS
TREAT ADVANCED BREAST CANCER

Reports from National Cancer Institute (NCI)-supported studies provide additional evidence that combinations of anti-cancer drugs are proving useful in treating advanced breast cancer.

Samuel G. Taylor, III, M.D., of Rush-Presbyterian-St. Luke's Hospital and George P. Canellos, M.D., of NCI's Medicine Branch, reported studies by NCI and by the Institute's Eastern Cooperative Oncology Group, in which drug combinations were used to treat women with recurrent and widespread stages of breast cancer.

In the cooperative study, 181 women at 20 hospitals were assigned at random to be treated with either phenylalanine mustard (PAM) or a three-drug combination of 5-fluorouracil, methotrexate, and cyclophosphamide. Most of the patients had suffered a relapse of cancer after initial treatment by surgery, and the majority had also been treated previously with radiation, hormones, or removal of hormone-secreting glands. None had been treated previously with anti-cancer drugs.

According to Dr. Canellos, after one and a quarter years of follow-up, about 60 percent of the patients who responded to the three- or single-drug treatments were still alive, compared with approximately 20 percent survival among patients who did not respond to drug treatment.

In preliminary results from the cooperative study, he said, the three-drug combination has produced significantly more partial and complete responses than have been achieved with the single-drug treatment. Among 90

(more)

Breast Cancer (Cont'd)

patients given the three-drug treatment, 48 (53 percent) achieved at least a partial response, including 12 patients (13 percent) with a complete disappearance of cancer. The most favorable responses occurred in patients whose disease had spread to the lymph nodes, soft tissue, or lungs.

Treatment with PAM produced a partial response in 22 (24 percent) of the 91 patients given this drug, including a complete response in three (three percent) of them.

The greater number of complete and partial responses among women treated with the three-drug combination has been responsible for improved overall survival among patients in this group, Dr. Canellos said. The survival rate for all patients treated with the drug combination was about 50 percent after one and a quarter years, as compared with a survival rate of about 28 percent after the same period for patients treated with PAM.

Co-authors of the cooperative study report, in addition to Drs. Taylor and Canellos, are Pierre R. Band, M.D., Alberta University School of Medicine, Edmonton, Alberta, Canada; and Stuart Pocock, Ph.D., State University of New York at Buffalo, Amherst, New York.

In the pilot study at NCI that led to the larger cooperative study, 33 women with advanced breast cancer have been treated with a combination of four drugs: methotrexate, 5-fluorouracil, cyclophosphamide, and prednisone. (See *NEFN*, February 25, 1974.) As in the cooperative study, most of the patients had suffered a relapse and had failed to respond to other modes of treatment.

Dr. Canellos, working with Vincent T. DeVita, Jr., M.D., G. Lennard

(more)

Breast Cancer (Cont'd)

Gold, M.D., Bruce A. Chabner, M.D., Philip S. Schein, M.D., and Robert C. Young, M.D., in the NCI Medicine Branch, reported that 23 (70 percent) of the 33 patients responded to the four-drug treatment, including a complete disappearance of cancer in seven (21 percent) of the patients.

Patients who responded to the drug combination have lived significantly longer than those who failed to respond, Dr. Canellos said. The 10 (30 percent) non-responders have had a median survival time of six months; that is, half of them died within six months after treatment began. The median survival time of the responders has not been reached but will be at least 16 months.

Dr. Canellos noted that phenylalanine mustard is also being evaluated in a randomized trial sponsored by NCI's National Surgical Adjuvant Breast Project. In that study, PAM is given after initial breast cancer surgery as a preventive agent in patients who have a high risk of relapse. If the single drug turns out to be effective, he said, then the improved results with three- and four-drug combinations in the ongoing NCI and cooperative studies would point the way toward an eventual trial of combination chemotherapy in the treatment of early breast cancer.

The studies were described at the 10th Annual Meeting of the American Society of Clinical Oncology and at the 65th Annual Meeting of the American Association for Cancer Research, held March 27 and 29, 1974, in Houston, Texas.

Research Advances

Lowers Sperm Count...

MALE CONTRACEPTIVE DRUG
SHOWS PROMISING RESULTS

First steps toward the development of a male contraceptive drug show that a drug combination can safely and effectively lower the production of sperm.

Researchers consider a sperm count of five million or less to be an important factor contributing to infertility. It is unknown whether reducing the sperm count to five million or less in normally fertile men will render them infertile.

These studies are being conducted by C. Alvin Paulsen, M.D., of the University of Washington, Seattle, under a contract with the Center for Population Research of the National Institute of Child Health and Human Development. The purpose of the present study is limited to determining if the sperm count can be safely and effectively lowered. Future studies will be aimed at achieving the total absence of sperm.

The response of the 92 participants in Dr. Paulsen's study undercuts some of the fears expressed about a contraceptive for men. The volunteers, 30 to 40 percent of whom are married, are primarily students 19 to 35 years old. They did not complain of a loss of libido (sex drive) while taking the drugs. In addition, the drop-out rate for the study was less than 10 percent, a fact which seems to indicate that men are more willing to personally use birth control measures than previously believed.

Following an initial three-month period in which the volunteers were examined thoroughly and monitored for information on their normal state of

(more)

Male Contraceptive (Cont'd)

health, they began a six-month period of drug treatment. The drugs the subjects received consisted of a weak male hormone pill taken daily and a potent male hormone injection given once a month. Because the present study did not attempt to test the contraceptive effectiveness of the drugs, the male volunteers were urged by the investigators to use other methods of birth control while participating in the study.

In order to determine the most effective drug combination, the investigators divided the volunteers into groups with different dose schedules. Dr. Paulsen reports that it took three to four months of treatment to lower the sperm counts of the subjects.

Most recent results of the study show that in the groups with effective drug combinations, 23 out of 37 men showed sperm counts of five million or less per ejaculation. The normal male produces 100 to 200 million sperm per ejaculation.

Another encouraging result is that, to date, no undesirable side effects have been observed. Dr. Paulsen bases this information on careful and continuous medical examination, including blood chemistry tests.

Following the drug treatment period, the volunteers will be closely monitored for a three-month recovery period, or until their sperm counts return to normal pre-treatment levels.

Dr. Paulsen presented these latest findings from his study of male contraceptive drugs in January, 1974.

Research Advances

HAIR SPRAY EXPOSURE
MAY PRESENT HAZARD

Exposure to three types of hair sprays for 20 seconds during clinical trials caused significant decreases of maximum expiratory flow rates and symptoms of chest tightness and respiratory distress in healthy men and women.

According to investigators Eugenija Zuskin, M.D., and Arend Bouhuys, M.D., Ph.D., these findings indicate that controlled inhalation studies in humans should be required as part of the toxicological evaluation of consumer products that may pose inhalation hazards.

Drs. Zuskin and Bouhuys of the Yale University Lung Research Center are supported in their research by a grant from the Pulmonary SCOR Program (Specialized Centers of Research) of the National Heart and Lung Institute.

The question of whether hair spray preparations cause lung disease has not been answered. However, informal reports from women who regularly experienced respiratory symptoms after using hair spray led the investigators to study whether such preparations could alter respiratory function in healthy persons.

Twenty subjects--14 men and six women, 22 to 38 years of age--participated in the single-blind trial of hair spray and placebo aerosols. None of the subjects used hair sprays regularly. The investigators purchased three hair sprays (A, B, and C) in a New Haven, Connecticut drug store: hair spray A contained povidone, B contained a resin, and C contained neither of these two substances. They attempted to assess the effects of continuous

(more)

Hair Spray (Cont'd)

spray exposure directed at the hair for 20 seconds, while the subject breathed quietly and kept the eyes closed.

As a result, the researchers found that hair sprays induce decreases in maximum expiratory flow rates, and, in some subjects, slight or moderate symptoms of chest tightness and respiratory distress. They found that the exposure has acute, short-lasting effects on the ventilatory function of the subjects. The effect of spray C could be suppressed by prior administration of atropine or an antihistamine drug.

This decrease in maximum flow rates at low lung volumes reflects constriction of the small airways, according to the investigators. At the same time, they report that peak expiratory flow decreased slightly or not at all, suggesting that large-airway narrowing is, at best, a minor factor in the effects of hair sprays.

The reduction in flow rates immediately after hair spray exposure was large and consistent. All subjects reacted to spray A, one subject did not respond to spray B, three of the 16 subjects complained of chest tightness and difficulty in breathing. Flow rates usually returned toward control values within two to three minutes. However, a residual effect was present 10 minutes after exposure.

According to Drs. Zuskin and Bouhuys, the design of their trials was kept simple, and the fact that the hair sprays were perfumed and could thus be distinguished from the placebo during exposure did not affect the validity of the data. Any of the chemical constituents of hair sprays, including perfumes, alone or in combination, may be responsible for the response.

(more)

Hair Spray (Cont'd)

According to the investigators, the data show that individual sensitivity to the airway-constrictor action of hair spray varies considerably. And, it is likely that the lack of evidence of excess lung disease among persons who regularly used hair spray in their jobs is due to the fact that sensitive persons avoid using this product, or, if beauticians, leave their jobs.

Since the majority of the subjects in the trials had measurable airway constriction after exposure, regular hair spray users may experience repeated subclinical airway narrowing, according to the researchers. It is possible, they suggest, that such repeated exposure to aerosol products such as hair sprays are causal factors in some cases of asthma and bronchitis.

The investigators published a report of their findings in the *New England Journal of Medicine*, March 21, 1974.

#

MONKEY CENSUS--The National Institutes of Health conducted a survey of worldwide primate populations to determine the future availability of primates for medical laboratory studies. A shortage of monkeys and apes for research is expected within the next five to 10 years. This could necessitate the breeding of all subhuman primates by investigators.

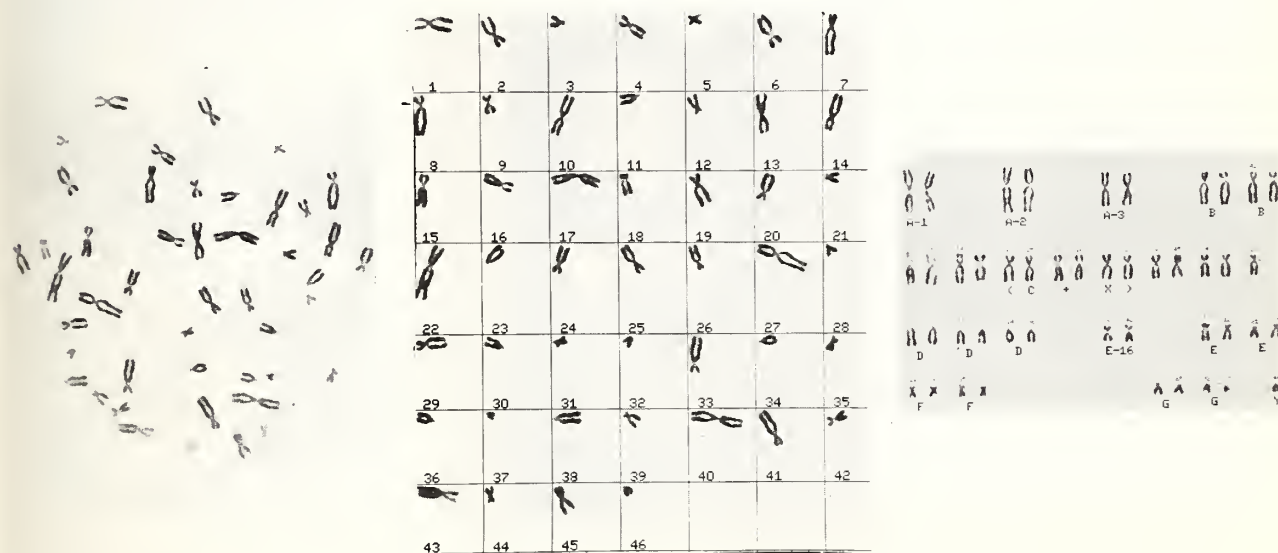
PRESSURE CHECKERS--The National Institutes of Health reports that some dentists and pharmacists are learning how to take blood pressure readings so that they can help Americans learn if they have high blood pressure. The sooner that elevated blood pressure is detected and treated, the better the outlook for the patient.

Photo Feature

COMPUTER SYSTEM SPEEDS
KARYOTYPE PREPARATION

Chromosome karyotypes (or patterns) which are used to diagnose several genetic diseases are difficult, time-consuming, and expensive to perform.

To make karyotypes more effectively, two California scientists are developing a microscope-computer combination that turns out, in minutes, pictorial karyotypes from random chromosomes. Their work is funded by contract with the National Institute of Child Health and Human Development.



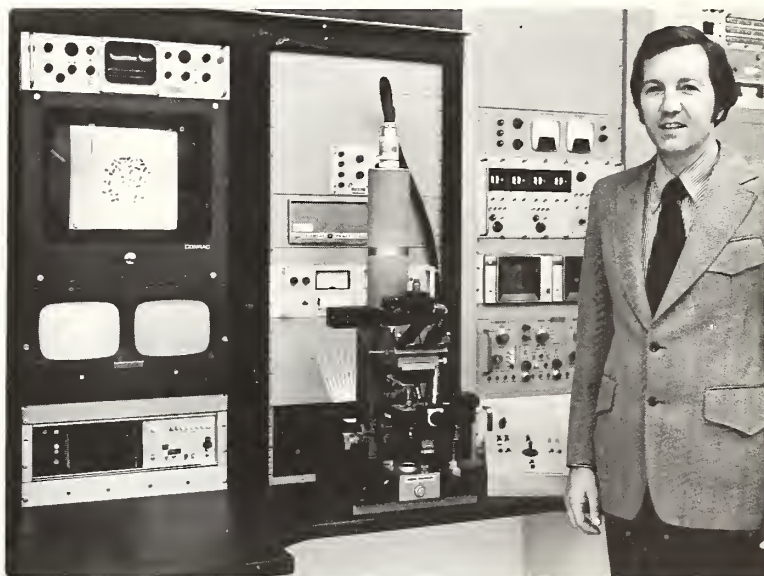
From a random spread (left photo) of 46 chromosomes the new Automated Light Microscope System scans and sorts each chromosome (center photo) so that the computer can orient and arrange them into the traditional karyotype pattern (right photo). The number above each chromosome is the order in which it was scanned. The code below classifies the chromosome. Two California scientists who have a contract with the National Institute of Child Health and Human Development are developing this system to speed the preparation of karyotypes. (NIH Photos #1224, 1225, 1226)

(more)

Karyotypes (Cont'd)

Kenneth R. Castleman, Ph.D., planned microscope and computer techniques to scan, evaluate, and arrange chromosomes. John H. Melnyk, Ph.D., is developing automatic techniques to prepare the chromosomal samples for scanning. They call their karyotype maker the Automated Light Microscope System (ALMS).

Dr. Castleman is a senior scientist at the Jet Propulsion Laboratory, Pasadena, while Dr. Melnyk is director of the Department of Developmental Cytogenetics at City of Hope Medical Center, Duarte.



Developers of a new microscope-computer system to quickly prepare chromosome karyotypes are John H. Melnyk, Ph.D. (left), shown at a traditional microscope and Kenneth R. Castleman, Ph.D., in front of the new system. By checking the screen (upper left) the operator can determine if the chromosome "spread" is suitable for further analysis. The system will karyotype conventionally stained as well as "banded" chromosomes. Dr. Melnyk works at City of Hope Medical Center, Duarte, California, while Dr. Castleman is at the Jet Propulsion Laboratory, Pasadena. (NIH Photos #1227, 1228)

Photo Feature

When Hospital Treatment Is Indicated...

PSORIASIS DAY CARE CENTERS
ELIMINATE HOSPITAL STAY

Two new psoriasis day care centers have recently opened to provide inpatient care at outpatient convenience.

Psoriasis, a common skin disorder that causes scaling, redness, and considerable disfigurement, affects an estimated six million Americans. While no permanent cure is yet known, applications of appropriate medications provide temporary control.

The majority of psoriasis patients do not require hospitalization, but for the five to 10 percent who do, the average hospital stay is two to four weeks, according to Eugene Farber, M.D., director of the new psoriasis day care center at Stanford University Hospital.



Dr. Eugene Farber, (right) director of Stanford University Medical Center's new psoriasis day care center, shows an ultraviolet treatment room to one of the Center's first patients, accompanied by Dr. William Watson (left), associate director of the day care center. (NIH Photo #1229)

(more)

Psoriasis (Cont'd)

David L. Cram, M.D., director of the psoriasis day care center at the University of California, San Francisco, believes that the day care method of treatment may be used throughout the United States for treatment of patients with psoriasis and other diseases which require intensive hospital-type treatment without the need of 24-hour special care. It is expected that these two new day care centers will be the first of many. Since the patient may not require expensive hospitalization, but can be treated intensively as an out-patient during the day, returning home each evening, Dr. Cram believes that day care centers can reduce the cost of hospital treatment by as much as 50 percent.

These pioneer psoriasis day care centers are staffed by dermatologists whose work is supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases.



The "home-like" atmosphere of the psoriasis day care center at the University of California, San Francisco, tends to create a positive mental attitude in the patients, according to Dr. David L. Cram (seated center), director of the center. Also pictured are Dr. M. B. Sulzberger (left), nurse Marie Cram, and Dr. William L. Epstein. (NIH Photo #1230)

Photo Feature

NORMAL VOLUNTEER PATIENTS
PARTICIPATE IN CC STUDIES

Since 1953, 5,250 healthy individuals have been admitted to the NIH Clinical Center as volunteer patients. This Normal Volunteer Program gives scientists the opportunity to observe the volunteers and compare them to the ill patients.

The volunteers often participate in two or more research studies simultaneously during their three to four month stay at NIH. Career assignments are arranged for volunteers who wish to explore medically-related occupations in the laboratories or hospital offices.



Gerald Koop, (left) a student from the Mennonite Central Committee, keeps one eye covered with a patch and taps his fingers on the table when he sees a small light flash on the oval screen. Donald Bergsma, M.D., National Eye Institute, records Gerald's normal reactions and then compares them to test results of patients with vision disorders. (NIH Photo #1231). The normal volunteer in the photo at right is lying on a hammock in the hot, dry atmosphere of the metabolic chamber while weight loss due to sweating is being recorded. Ronald Thompson, Ph.D., National Institute of Arthritis, Metabolism, and Digestive Diseases, notes the progress of the study. (NIH Photo #1232)



April 10, 1974

Medical News Tip

MISSING ENZYMES--Replacement of deficient or missing enzymes holds promise for the cure of disorders such as Lesch-Nyhan disease, in which the mentally retarded patients tend to mutilate their own bodies by scratching and biting.

Investigators have learned that when cells from Lesch-Nyhan patients are mixed with those from normal persons, the affected cells begin to metabolize normally. This "metabolic cooperation" suggests therapy may be possible in the future.

Enzyme replacement therapy is also being studied in Sanfilippo disease. In this disorder, a specific substance is stored in the brain in abnormal quantities because an enzyme needed to break it down is missing.

In the laboratory, when the purified enzyme is added to the enzyme-deficient cells from Sanfilippo patients, cell growth is normal. When the enzyme is not present, however, build-up occurs in the cells. Investigators are also testing the effects of the purified enzyme in Sanfilippo patients by administering it in normal blood plasma.

For more information about enzyme replacement therapy, contact:

National Institute of Child Health and Human Development
National Institutes of Health
Landow Building, Room A804
Bethesda, MD 20014
Phone: (301) 496-5133

News Releases Issued

MRFIT--Screening and enrollment of men between the ages of 35-57 to take part in a six-year cardiovascular study is underway in 20 centers throughout the United States. The Multiple Risk Factor Intervention Trial (MRFIT) will assess the effectiveness of measures to reduce elevated blood cholesterol, high blood pressure, and cigarette smoking in preventing first heart attacks and reducing death rates from cardiovascular diseases. These three factors are strongly associated with increased susceptibility to premature coronary heart disease and such consequences as heart attacks and sudden cardiac deaths. It is estimated that approximately 80 percent of death and disability from coronary heart disease occurs among individuals having one or more of these risk factors working against them.

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See page 10

RESEARCH ADVANCES:

	<u>Page</u>
Group of Antibiotic Drugs Acts Against Cancer Viruses.....	1
Scientists Report Progress in Vaccines Against Tooth Decay.....	4
Fructose Equals Sucrose in Causing Tooth Decay.....	6
Fluoride in Drinking Water Provides More Protection Than in Enamel.....	8

NEWS & PHOTO FEATURES:

Frederick Center Produces Viruses For Cancer Studies.....	10
Scientist Couple Studies Neural Basis of Touching.....	12

NEW PUBLICATION:

<i>Sinusitis</i>	13
------------------------	----

NEWS RELEASES ISSUED:

Anti-Cancer Drugs, Peptic Ulcers, Dental Awards.....	14
--	----

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Research Advances

GROUP OF ANTIBIOTIC DRUGS
ACTS AGAINST CANCER VIRUSES

A group of antibiotic drugs has been found unexpectedly to be active against viruses that cause cancer in animals.

A team of scientists from the National Cancer Institute (NCI) and Litton Bionetics, Inc., Bethesda, Maryland, made the discovery with a newly-developed test system for antiviral activity. The finding raises the possibility that antiviral properties may be more common among antibiotics than previously thought, according to Timothy E. O'Connor, Ph.D., NCI Coordinator for Molecular Control.

This work was conducted by Dr. O'Connor and Pauline Schiop-Stansly of NCI and V. Sager Sethi, Ph.D., Ahmed Hadidi, Ph.D., and Paul Okano, Ph.D., of Litton Bionetics.

The scientists found that four rifamycin antibiotics prevented the cancerous transformation of human embryonic spleen cells by the Synder-Theilen strain of feline (cat) sarcoma virus. The virus-induced transformation was indicated by the appearance of clumps of multiplying cells among human cells grown in laboratory culture dishes. The rifamycin drugs also blocked a similar transformation of mouse 3T3 cells by the Moloney mouse sarcoma virus. Both the cat and mouse sarcoma viruses have cores of RNA (ribonucleic acid).

The four rifamycin antibiotics (termed rifamycin B, rifamycin O, rifamycin S, and rifamycin SV) are naturally-occurring in secretions by *Streptomyces mediterranei* bacteria. Rifamycins S and SV gave the strongest inhibition of cell transformation.

(more)

Antibiotic Drugs (Cont'd)

Dr. O'Connor explained that his team also tested rifampicin and other man-made derivatives of rifamycin SV. A few of the compounds had moderate antiviral activity comparable to rifamycin B or O, while others had negligible activity. The NCI scientist noted that these synthetic compounds have been studied intensively in recent years as inhibitors of reverse transcriptase (RNA-dependent DNA polymerase), an enzyme believed to play a critical role in the infection of cells by RNA viruses.

However, the rifamycins have little effect on reverse transcriptase. According to Dr. O'Connor the present research indicates that the cancerous transformation of cells by RNA viruses can be blocked by compounds that are ineffective against the reverse transcriptase enzyme.

In further tests, the scientists found that rifamycin S was particularly effective in preventing production of viruses by mouse 3T3 cells freshly infected with the Moloney mouse sarcoma virus. The drug had little effect, however, on virus production that was well-established in mouse cells prior to addition of the drug. From these and related observations, Dr. O'Connor concluded that the drug's antiviral effect occurs at some time between viral penetration of the cell and complete reproduction of the virus in the cell.

The NCI scientist noted that the rifamycin drugs have been found to have comparable effects on cancerous cells and actively growing normal cells and thus do not appear to be useful specifically as anti-cancer agents. However, he speculated that the rifamycins might be useful in controlling the spread of cancer in the body if RNA viruses are found to contribute to spread from an initial cancer site.

(more)

Antibiotic Drugs (Cont'd)

Dr. O'Connor suggested that tests of other antibiotics might yield additional compounds with antiviral activity. He said other scientists have found antiviral activity with antibiotics from two other species of *Streptomyces* bacteria: streptovaricins from *Streptomyces spectabilis* and streptonigrin from *Streptomyces flocculus*. Streptonigrin has a molecular structure different from the streptovaricins and rifamycins, which supports the possibility that antiviral drugs may be found more widely.

The NCI and Bionetics scientists used a test system developed with guidance from NCI's Molecular Control Working Group. The Molecular Control Working Group, chaired by Dr. O'Connor, is a body of Government and non-Government scientists that advises NCI on findings in the field of molecular biology that may lead to new approaches in cancer treatment, detection, or other aspects of cancer control and prevention.

Dr. O'Connor described this research at the 65th Annual Meeting of the American Association for Cancer Research in Houston, Texas, March 28, 1974.

#

TOLL OF STROKES--About 400,000 Americans will suffer a major stroke this year, predicts the National Institutes of Health. About half of these victims will die because of the stroke, while many of the others will begin long periods of disability and dependency.

Research Advances

SCIENTISTS REPORT PROGRESS
IN VACCINES AGAINST TOOTH DECAY

Vaccines can help prevent organisms suspected of causing tooth decay from colonizing on monkey's teeth. Bacterial colonization on teeth in a microbial mat called dental plaque is necessary before tooth decay occurs.

Fred G. Emmings, D.D.S., Ph.D., R. Todd Evans, Ph.D., and Robert J. Genco, D.D.S., Ph.D., of the State University of New York in Buffalo, injected anesthetized animals with killed *Streptococcus mutans* (*S. mutans*). The injections were made into the ducts of the parotid salivary gland (one of the major pairs of salivary glands). The vaccine stimulated production of salivary antibodies against the decay-causing *S. mutans* and thereby dramatically reduced the amount of *S. mutans* in dental plaque. This work was supported in part by grants from the National Institute of Dental Research (NIDR).

Although this achievement is encouraging, Dr. Emmings believes that much work remains to be done before a vaccine can be tested in man. Research must first prove that a vaccine against only one organism will safely and significantly decrease decay. Also, scientists must find other routes of administration because injections into salivary glands or ducts are not without pain and risk of infection.

Previously, a British scientist, William H. Bowen, Ph.D., now at NIDR, did reduce the number and severity of decay lesions in monkeys by intravenous injection of live *S. mutans*. However, such a vaccine is too dangerous for people because the organism can produce heart damage.

(more)

Vaccines (Cont'd)

Dr. Emmings' findings suggest that Dr. Bowen's vaccine may have reduced decay by stimulating production of salivary antibodies against *S. mutans* and thereby controlling colonization on teeth.

Vaccine progress is based on years of painstaking basic research. Scientists realized that antibodies in saliva rather than those in blood must be relied upon to fight decay-causing organisms because crowns of teeth are bathed in saliva but not in blood. Dr. Genco's team at the State University of New York, Buffalo, has found that the salivary immune system is distinct from that in blood and was among the first to stimulate that system.

Dr. Emmings' findings also help explain in part the behavior of *S. mutans* in human mouths. The organisms generally are present in decayed areas in teeth, but often are not in the plaque on other surfaces of that same tooth or on other teeth in the same person's mouth. Furthermore, the organism cannot be easily implanted in human mouths. Naturally-occurring salivary antibodies against *S. mutans* may be an explanation for the organisms' behavior.

Most wild monkeys do not harbor *S. mutans* normally and, therefore, have no antibodies against them. Consequently, when Dr. Emmings infected control animals with the organism it thrived. Within two months, *S. mutans* comprised up to half of the streptococcal organisms in the dental plaque. The picture was different in the immunized monkeys. The organisms were highly localized as they are in human mouths.

The investigators presented their findings at the International Association for Dental Research meeting, in Atlanta, Georgia, March 23, 1974.

Research Advances

Studies in Humans...

FRUCTOSE EQUALS SUCROSE
IN CAUSING TOOTH DECAY

Fructose (fruit sugar) is equal to sucrose (table sugar) in contributing to tooth decay on the smooth surfaces of crowns in humans, according to dental scientists at the University of Alabama, Birmingham.

Theodore Koulourides, D.M.D., and associates at the University's Dental Institute, studied six sugars and evaluated their contribution to cariogenicity in humans. The investigators rank the other four sugars in order of descending effects on dental decay as follows:

- melibiose (from molasses)
- raffinose (from sugar beets and cottonseed oil)
- sorbitol (from the sorbus tree)
- xylitol (wood sugar)

Dr. Koulourides observed the effects of the substances on dental decay by mounting slabs of sound enamel from cattle on a denture or hook fitted around the teeth of human volunteers. The hardness of the enamel is measured in terms of its resistance to puncture by a diamond punch. Then, the slab is covered with dacron gauze to trap the volunteer's bacteria, enhance colonization, and form plaque quickly. The slab is kept in the mouth for a week. However, it is removed four times a day and immersed for 10 minutes in a solution of the sugar being tested.

In this study, Dr. Koulourides reports that a three percent sucrose solution doubled the individual's potential for decay as well as a 10 percent solution did. Therefore, all sugars were tested against the three percent standard.

(more)

Tooth Decay (Cont'd)

At the end of seven days, the researchers recorded any change in the ability of the enamel slab to resist puncture pressure. The softer the enamel, the greater potential for decay. This slight softening of enamel by bacterial acids can be verified microscopically and can easily be reversed at this early stage. Severe decay, however, which is visible to the naked eye as a cavity, is irreversible.

Dr. Koulourides reports that xylitol seems to have little or no ability to encourage decay. Therefore, it might possibly be a substitute for table sugar, especially in snack foods, if it has no adverse effect on humans. However, other scientists have reported that rats do not thrive on xylitol.

Dr. Koulourides and associates Rupert Bodden, D.M.D., Stanley Keller, D.M.D., and Lincoln Manson-Hing, D.M.D., reported their findings at the International Association for Dental Research meeting, in Atlanta, Georgia, March 23, 1974. These sugar studies were supported by a contract from the National Institute of Dental Research.

#

LITTLE STROKES--A little stroke can come as an attack of dizziness, vomiting, blackout, or falling which may leave the victim with a temporary or permanent disability, according to the National Institutes of Health. Anyone who suspects a little stroke has occurred should seek immediate medical advice.

Research Advances

FLUORIDE IN DRINKING WATER PROVIDES
MORE PROTECTION THAN FLUORIDE IN ENAMEL

Frequent exposure to low levels of fluoride in drinking water gives rats much greater protection against tooth decay than the incorporation of a large amount of fluoride into enamel.

This evidence was presented by Rachel H. Larson, Ph.D., and assistants Harold R. Englander, D.D.S., and Rickley S. Senning, M.P.H., of the National Institute of Dental Research, and James R. Mellberg of the Kendall Company, Barrington, Illinois.

In the experiments, Dr. Larson divided into two groups weanling rats of the same age and strain with erupted first and second molars. Both groups received a low-fluoride, starch diet that does not encourage decay for a pre-test period of one week. However, one group drank water without any fluoride; the water for the other group was very strongly fluoridated.

After this first week, the researchers analysed the tooth enamel in representative animals from both groups. They found only 375 parts per million (ppm) of fluoride in the outer enamel of rats in the first group, but noted six and a half times as much fluoride in the enamel of the second group.

All animals then were infected with a bacterium (*Streptococcus mutans*) found in human cavities and known to cause decay in germfree animals. The investigators fed the rats a sugar-rich diet to promote dental decay for the next 56 days (the caries test period). The original groups were subdivided so that half of each group received water without fluoride while the other half got water to which only 10 ppm of sodium fluoride were added. (This is

(more)

Fluoride (Cont'd)

less fluoride than is used in most rat studies.) At the end of the experiment, the rats' teeth were analysed for fluoride and the decayed areas were counted.

A comparison of the two groups of animals given no fluoride in the drinking water during the caries test period showed that those never having received fluoride developed more than twice as many decayed areas (58.4) as those receiving highly fluoridated water for one week prior to the test period (27.5 carious areas). However, animals receiving 10 ppm fluoride in water during the test period developed an even smaller number of decayed areas: 16.0 for those having no other fluoride, and 3.3 for those having highly fluoridated water for the week prior to the test period.

These results are especially interesting, Dr. Larson believes, because the animals on 10 ppm fluoride showed very little increase of fluoride in their enamel as compared with animals having no fluoride during the test period.

Although scientists still do not understand the way fluoride works, these experiments show clearly that even though internal incorporation of considerable fluoride into enamel gives some protection against tooth decay, far more protection comes to the animals from daily consumption of properly fluoridated water when other factors such as heredity, diet, and bacterial infections remain the same.

The investigators presented their findings at the International Association for Dental Research meeting, March 24, 1974.

Photo Feature

FREDERICK CENTER PRODUCES
VIRUSES FOR CANCER STUDIES

The virus production laboratory at the Frederick Cancer Research Center will soon manufacture 250 liters of virus material per week for use in cancer virus studies at the Center and at other laboratories supported by the Virus Cancer Program of the National Cancer Institute (NCI). The research of this program includes work in laboratory-grown cells and in experimental animals, as well as other specialized biochemical studies on cancer.

The Center is capable of large-scale production in tissue culture of proven cancer-causing viruses, such as those from chickens, mice, rats, hamsters, cats, and monkeys. It also develops new procedures for production of candidate human tumor viruses isolated from human tumor tissue.



A small number of cells infected with virus are put in bottles with a liquid nutrient. The bottles are then placed on roller racks (left) designed to keep them rotating so that cultured cells can grow evenly over the inside surface of the glass. After several days of continuous growth and multiplication, the fluids are harvested. At this stage, the fluids contain a large number of virus particles. (NIH Photo #1233)

(more)

Cancer Center (Cont'd)

Virus studies are only a part of the work at the Center which is operated for NCI by Litton Bionetics, Inc. Research is under way on chemical causes of cancer, advanced techniques of animal holding and breeding, and environmental safety measures.

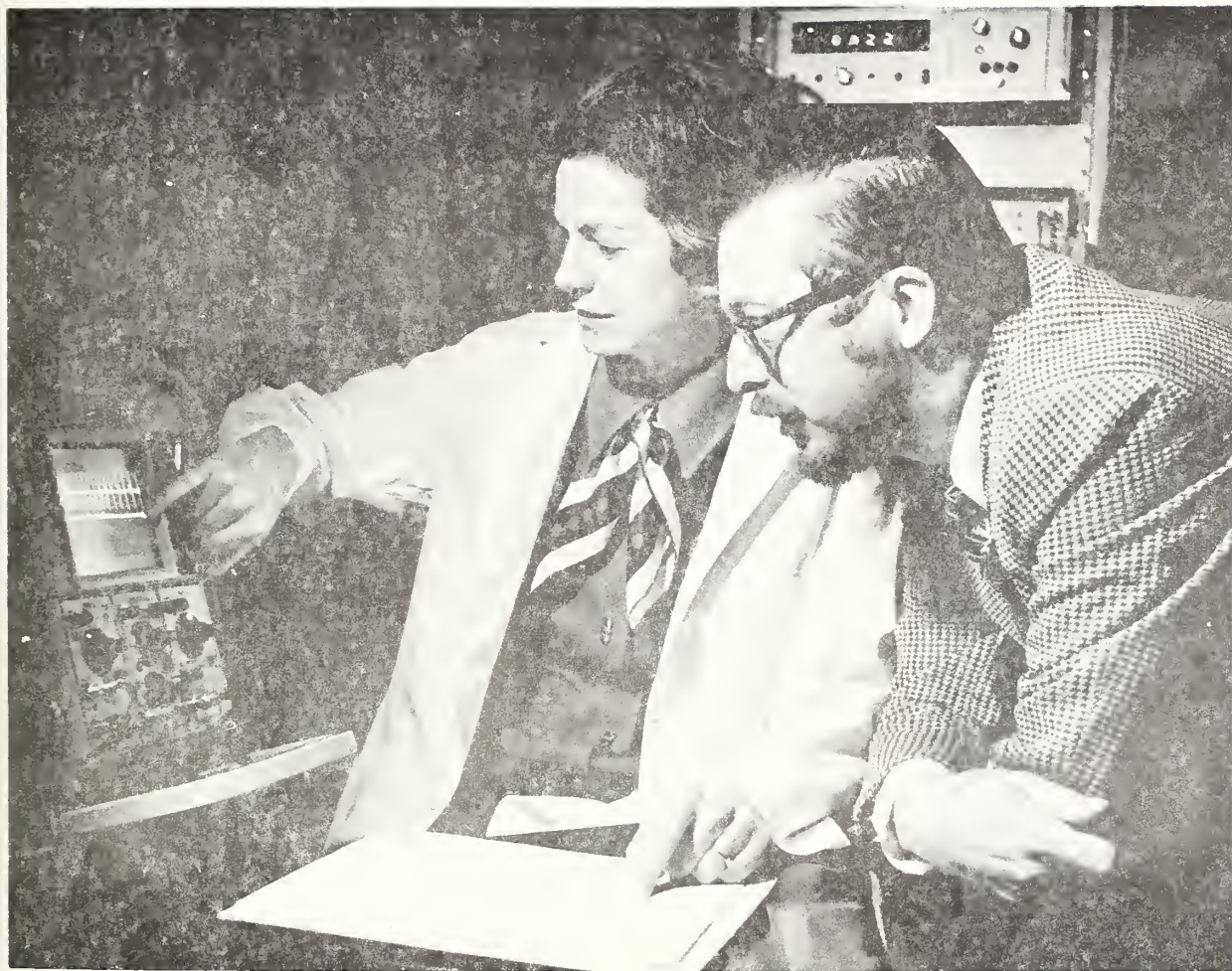


The harvested fluids are concentrated 1,000-fold by a process known as density-gradient centrifugation. This process separates cellular material, nutrients, and virus particles into distinct bands based on differences in weight and density. One of the ultracentrifuges used for this purpose (pictured here) rotates at speeds up to 35,000 rpm, achieving a gravitational force of over 90,000 x g. The final product contains nearly one billion virus particles per milliliter of fluid.

(NIH Photo #1234)



Photo Feature

SCIENTIST COUPLE STUDIES
NEURAL BASIS OF TOUCHING

Lillian M. Pubols, Ph.D., and B. H. Pubols, Jr., Ph.D., of the Pennsylvania State University, Hershey, are studying the neural basis of the sense of touch. The husband-wife team uses themselves as subjects to determine what part of the nervous system are involved in the sense of touch, and how humans can detect where and how strongly they have been touched. The couple also studies the specialized "tactile organ systems" of spider monkey tails and opossum whiskers. They are shown examining oscilloscope traces that depict the electrical response of a raccoon nerve fiber when the skin of its forepaw is touched. Their research is supported by the National Institute of Neurological Diseases and Stroke. The Pubols met at a University of Wisconsin medical research laboratory. (NIH Photo #1235)

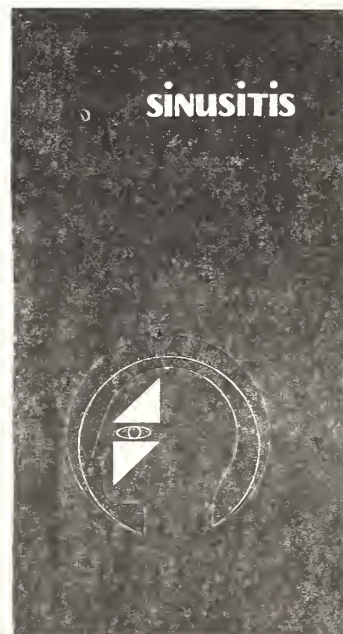
New Publication:*Sinusitis*

Inflammation of a sinus is a miserably painful condition. This condition, sinusitis, usually occurs in one or more sinus cavities located within the skull surrounding the nose.

Pain when the forehead is touched may indicate inflammation of the frontal sinuses, which are located over the eyes in the brow area. Infection in the maxillary sinuses, which are inside each cheekbone, can cause the upper jaw and teeth to ache and the cheeks to become tender to the touch.

Sinusitis often causes swelling of the eyelids and tissues around the eyes, pain between the eyes, and tenderness when the sides of the nose are touched. Infected sinuses also cause postnasal drip, which can lead to irritation of the throat or membranes lining the larynx or upper windpipe.

The National Institute of Allergy and Infectious Diseases (NIAID) has released a new booklet, *Sinusitis*, giving information about symptoms, causes, prevention, and treatment of sinusitis.



Science writers can obtain a free copy of the publication from:

NIAID
National Institutes of Health
Bldg. 31, Room 7A-32
Bethesda, MD 20014
Phone: (301) 496-5717

News Releases and Announcements Issued

ANTI-CANCER DRUGS--The National Cancer Institute (NCI) has awarded a \$3,794,147 prime contract for evaluating the safety and side-effects of potential new anti-cancer drugs. The contractor, Battelle Memorial Institute's Columbus Laboratories, Columbus, Ohio, will be responsible for day-to-day management of the NCI toxicology program. Battelle-Columbus scientists will work closely with NCI's Laboratory of Toxicology, which will monitor the contractor's performance and continue to be responsible for critical decisions. Under the terms of the contract, Battelle's Columbus Laboratories will establish a network of subcontracting laboratories, the number depending on the availability of new drugs ready for toxicology testing.

PEPTIC ULCERS--An initial grant of \$890,676 has been awarded to the University of California, Los Angeles, School of Medicine to study peptic ulcers. The five-year study awarded by the National Institute of Arthritis, Metabolism, and Digestive Diseases will set up a Peptic Ulcer Center at UCLA, involve 10 key investigators with multidisciplinary expertise, and may ultimately cost more than \$4 million.

DENTAL AWARDS--The Special Dental Research Award (SDRA) Program of the National Institute of Dental Research (NIDR) has been modified to make the special research grants more useful to the newly-trained investigator. New applicants for this type of research grant may now request up to \$10,000 for direct costs. (The maximum for existing awards is \$7,500.) SDRA' are made

(more)

Dental Awards (Cont'd)

to newly-trained investigators with no more than four years of experience beyond completion of research training. Projects relate to such areas as periodontal, soft tissue, and oral neoplastic diseases; dental caries; craniofacial anomalies; dental pain; and restorative and prosthetic materials.

To obtain further information on NIDR program interests, contact:

Extramural Programs, NIDR, Room 503, Westwood Building, Bethesda, Maryland 20014.

CANCER DEATHS--Statistics on cancer deaths in each of the 3,056 counties of the United States have been published for the first time in a new National Cancer Institute (NCI) compendium, *U.S. Cancer Mortality by County: 1950-1969*. Previously such statistics had been available only by region or by state. The 729-page volume lists the total number of cancer deaths for each of 34 body-sites according to sex and race (whites and non-whites) for each county over the 20-year period. In addition, age-adjusted cancer death rates per 100,000 persons are given. Information for the new NCI publication was obtained from a series of magnetic tapes provided by the National Center for Health Statistics. *U.S. Cancer Mortality by County: 1950-1969*--DHEW Publication No. (NIH) 74-615--is available from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. The price is \$9.00.

#

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May 10, 1974



See page 13

Page

RESEARCH ADVANCES:

Adults Need As Much Calcium as Children.....	1
Study Offers Clues to Antibody Diversity.....	4
Adhesive Sealant Prevents Tooth Decay.....	7

NEWS & PHOTO FEATURES:

Scientists Study Poison From Frogs.....	9
Girl Recovers From Burns.....	12
DRS Revises NIH Rodent Catalog.....	13

MEDICAL NEWS TIP:

Aging and Stress.....	15
-----------------------	----

NEW PUBLICATION:

<i>What Are the Facts About Genetic Disease?</i>	16
--	----

NEWS RELEASES ISSUED:

Cancer-Causing Chemicals, Radiation Treatment.....	17
--	----

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Research Advances

ADULTS NEED AS MUCH
CALCIUM AS CHILDREN

Adults may need to consume as much calcium as children, according to Herta Spencer, M.D., a grantee of the National Institute of Dental Research.

Results of Dr. Spencer's 92 metabolic studies carried out in men under controlled dietary conditions showed that a level of 1200 mg of calcium per day is most desirable. (This is the amount in a balanced diet including three glasses of milk per day.) A daily intake of 800 mg of calcium (the amount in a balanced diet and two glasses of milk per day) was sufficient to attain calcium equilibrium for most people in the study group. However, several patients receiving that intake had a negative calcium balance; that is, they excreted more calcium in the urine and in the stools than they were consuming.

When the body receives too little daily calcium, the element will be removed from its storage depots in bone to maintain normal blood levels. Years of chronic calcium depletion may lead to osteoporosis, a condition in which the vertebrae and long bones become porous and fragile. In advanced stages, the condition is painful and disabling. Osteoporosis is especially common in women after menopause, but it is also encountered in men, particularly in patients with chronic alcoholism.

In order to determine the calcium intake on which either calcium equilibrium or a positive calcium balance is attained, Dr. Spencer carried out her physiological studies during different intakes of calcium in adult, fully ambulatory males on a constant metabolic diet. The study group included patients who did not have any evidence of osteoporosis and those who had

(more)

Calcium (Cont'd)

advanced osteoporosis with or without symptoms.

The calcium intakes used in these studies were: a low calcium intake of 200 mg per day, a normal calcium intake of 800 mg per day, two intermediate levels of calcium of 1200 and 1400 mg per day, and a high calcium intake of 2200 mg per day. The low calcium intake was contained in the constant metabolic diet; higher calcium intakes were attained by adding calcium gluconate tablets or milk to this diet.

Dr. Spencer found that the entire group of patients tested, including those with osteoporosis, achieved positive balances when their calcium intake was raised to the 1200 mg per day level. Calcium intakes higher than that level did not increase calcium retention for any of the people tested.

When calcium was given as milk, the retention was greater than from calcium gluconate tablets, both in patients with osteoporosis and in those without this condition. Milk is more effective probably because it contains phosphorus, known to play a role in calcium metabolism. Dr. Spencer showed that phosphorus, when given as glycerophosphate along with calcium tablets, decreases the loss of calcium in urine. Retention improved, and reached the levels attained with milk.

Calcium, a vital element for many cell functions and for forming and maintaining the normal bone and tooth structure, is present in small amounts in certain vegetables and cereal. However, the chief source of calcium is milk. It is an accepted fact that children and pregnant women require high levels of calcium. The current study adds evidence that an adequate intake also is desirable for adults and that patients with osteoporosis require more calcium than those without the condition.

(more)

Calcium (Cont'd)

According to Dr. Spencer, "Because it is not yet possible to predict the development of osteoporosis and because of the difficulty in diagnosing and treating this condition, it is desirable for adults to consume 1200 mg of calcium daily rather than the presently recommended dietary allowance of 800 mg per day."

Collaborating with Dr. Spencer in this study at the Veterans Administration Hospital, Hines, Illinois, were Lois Kramer, Clemontain Norris, and Dace Osis. The research was also supported by the National Dairy Council.

#

AMNIOCENTESIS--Amniocentesis was first developed in the latter part of the last century. It consists of obtaining amniotic fluid through the insertion of a needle into the amniotic cavity, according to the National Institutes of Health.

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TRANSPLANTS--Kidney transplants were sporadically attempted for almost 40 years before the first successful transplant was accomplished between identical twins, according to the National Institutes of Health.

Research Advances

STUDY OFFERS CLUES
TO ANTIBODY DIVERSITY

A team of NIH scientists has come up with new clues to one of the key mysteries of immunology--the basis of antibody diversity.

Working with closely related strains of inbred mice, the investigators from the National Institute of Allergy and Infectious Diseases (NIAID) and the National Cancer Institute (NCI) found that the ability of the mice to manufacture a particular type of antibody was closely linked to the presence of certain genetic factors.

Antibodies are protein molecules which arise in vertebrates (including humans) when foreign substances (antigens) are introduced into the body. Antibodies combine with corresponding antigens in lock-and-key fashion and help to inactivate them and eliminate them from the body.

A single animal seems to be capable of producing thousands of different antibodies in response to a similar number of different antigens. It may be possible, therefore, that this animal possesses, from birth, a genetic blueprint for every one of the antibodies it is potentially able to produce. Or, it may be necessary to invoke some special mechanism to explain this enormous capability.

In an attempt to solve these mysteries relating to the genetic basis of antibody diversity, the NIH researchers studied a particular type of antibody, known as the T15 idiotype, initially obtained from several independently-arising tumors of mouse antibody-forming cells. The T15 antibodies are known to combine with an antigen called phosphorylcholine which is present in certain bacteria.

(more)



Antibody Diversity (Cont'd)

In the present study, the investigators looked for T15 antibodies in sera of various inbred strains of mice, many of which were closely related. They found significant levels of T15 in several of the strains, but not in others. Germ-free animals of a T15-producing strain did not have the antibody in their sera; however, when they were placed in a normal (germ containing) environment, they soon produced it. When the scientists specifically immunized T15-producing mice with phosphorylcholine-containing bacteria, the amount of T15 antibody in the animals' sera increased.

Most important, only strains of mice carrying a particular set of genes relating to antibody structure turned out to be T15 producers, although not all strains carrying these genes produced the antibody. It is known that the genes in question do not themselves direct formation of T15 antibodies. Rather, the investigators demonstrated that these genes are located close to those that do control T15 formation.

The finding that the ability to produce T15 antibodies is inherited in such a clearcut fashion tends to support the so-called "germ line theory" of antibody diversity. This theory holds that mice and men (along with other vertebrates) possess from birth all the genetic instructions for antibody formation that they will ever have.

Viewed broadly, this work represents an early step toward defining the genetic basis of antibody diversity. Growing knowledge of this subject will lead to a better understanding of such phenomena as inherited variations in resistance to infectious diseases. With this increased understanding, scientists may be able to enhance disease resistance in some instances.

(more)



Antibody Diversity (Cont'd)

Rose Lieberman, William Humphrey, Jr., and Stuart Rudikoff, Ph.D., of NIAID and Michael Potter, M.D., and Elizabeth B. Mushinski of NCI presented their findings on April 8, 1974, at the annual meeting of the Federation of American Societies for Experimental Biology, Atlantic City. The work appeared in the April 1974 issue of *The Journal of Experimental Medicine*.

#

CANCER AND VIRUSES--The National Institutes of Health has uncovered strong evidence relating viruses to human cancer. Some findings suggest that an enzyme in the human leukemic cells may be of viral origin, although the evidence does not indicate that viruses cause the disease.

HODGKIN'S DISEASE--The National Institutes of Health uses a special four-drug combination treatment for patients with Hodgkin's disease. Of every 100 patients so treated, 80 went into complete remission; 65 of the 100 can expect to remain alive, and 40 will be continuously free of disease after five years.



Research Advances

Chewing Surface Decay...

ADHESIVE SEALANT
PREVENTS TOOTH DECAY

A single application of an adhesive sealant was 67 percent effective in preventing tooth decay on chewing surfaces. Additionally, the sealant was completely retained in 73 percent of treated teeth after two years of study.

Herschel S. Horowitz, D.D.S., of the National Caries Program, National Institute of Dental Research (NIDR), reports these interim findings from a three-year study in Kalispell, Montana, a non-fluoridated community.

Occlusal surfaces of teeth often have deep pits and fissures in which food and debris collect. Bacterial growth on this residue favors the occurrence of decay. Adhesive sealants are designed to fill and occlude these natural stagnation areas in teeth. Current accepted therapy for controlling pit and fissure decay relies mainly on the use of fluorides, but, because of the high decay susceptibility of these tooth sites, fluoride procedures have achieved limited success. A new and more effective approach to the prevention of pit and fissure decay would have great importance in the practice of preventive dentistry. Adhesive sealants hold such promise, and are therefore receiving widespread attention and study.

Dr. Horowitz, chief, Community Program Section, and his co-investigators, Stanley B. Heifetz, D.D.S., of the same program and Robert J. McCune, D.D.S., formerly of NIDR and now with the Johnson and Johnson Company, based their results on findings on 350 children in kindergarten, first, fifth, and sixth grades when the study began.

(more)



Adhesive Sealants (Cont'd)

Participants received the sealant treatment on only one side of the mouth and comparisons were made with corresponding teeth on the untreated side. The adhesive sealant was applied by the dentists in a procedure consisting of cleaning the teeth, thoroughly drying them, conditioning the surface with a mild acid solution, painting the adhesive in liquid form on to the surface, and hardening it with ultraviolet light.

The investigators report additionally that the sealant's effectiveness was similar in younger and older children and in upper and lower teeth. However, bicuspid's tended to show greater benefits than molars. Concerning the loss of sealant, the investigators noted that 11 percent of the treated teeth had lost a portion of the originally-placed sealant and 16 percent had the sealant completely missing.

Dr. Horowitz says that the two-year findings in Kalispell are less striking than those observed in the first, two-year study with the adhesive in Rochester, New York, a fluoridated community. Nevertheless, he looks upon the Kalispell findings to date as encouraging and offering corroborative evidence of the adhesive sealant's effectiveness.

The scientists presented their findings at the International Association for Dental Research meeting, in Atlanta, Georgia, March 23, 1974.



Photo Feature

For 10 Years...

SCIENTISTS STUDY POISON FROM FROGS

The poisons in skin secretions of certain colorful frogs may one day lead to important new pharmaceuticals.

Since 1964, John W. Daly, Ph.D., and Bernhard Witkop, Ph.D., of the National Institute of Arthritis, Metabolism, and Digestive Diseases have been isolating the poison called batrachotoxin from the Colombian kokoi frog. They provide the poison to laboratories all over the world for fundamental studies on the mechanisms involved in its action on nerves and muscles.

Batrachotoxin is one of the most toxic chemicals known to man. In fact, one milligram is sufficient to kill 50,000 mice. It causes an irreversible blockade of the transmission of nerve impulses to muscles, elicits cardiac arrhythmias, and leads to death by cardiac arrest.

Pioneering studies of E.X. Albuquerque, M.D., Ph.D., and his colleagues at the State University of New York at Buffalo established batrachotoxin as an important tool for research on electrical activity in nerve and muscle.

The poison elicits changes in the outer membrane of nerve and muscle cells causing
(more)

*The kokoi frog produces an extremely powerful poison in its skin glands, which it uses to protect itself against predators. The potency of this poison was recognized centuries ago by Indians of Colombia who still use it to poison their blow darts. The young frog shown at the right was born at NIH. Adults of this species are only slightly more than an inch in length.
(NIH Photo #1236)*



Frogs (Cont'd)

sodium ions present outside the cell to move into the cell. The toxin is therefore useful in studying how electrical signals are normally generated through similar changes in sodium ion movement and how these signals move along nerve fibers to ultimately cause the release of transmitter substances and muscle contracture.

In heart preparations, batrachotoxin initially increases the force of contraction. Study of this action may one day lead to a new drug for the treatment of cardiac insufficiency.

Chemically, batrachotoxin was shown to be a unique and complex nitrogen-containing substance, which is distantly related in structure to certain steroid hormones.

In order to obtain further extracts from the skins of the kokoi frog, Dr. Daly and Charles W. Myers, Ph.D., of the American Museum of Natural History, traveled to the Pacific rain forests of Colombia. On these trips,

The highly poisonous kokoi frogs are collected in Pacific rain forests in Colombia. Dr. Daly uses mask and gloves to avoid contact with the poison while he skins the frogs and stores the skins in alcohol for future purification at NIH. The frogs of this family are active by day and their distinctive calls can be heard for some distance in the forest.
(NIH Photo #1237)

(more)



Frogs (Cont'd)

they prepared extracts of various other species of dendrobatid frogs, some of which have yielded new substances, whose chemical nature and biological properties are proving as interesting as that of batrachotoxin.

#

MONGOLISM--Maternal age is correlated with genetic defects in children. The chances of giving birth to a child with Down's syndrome are five to ten times higher for women over 35, according to the National Institutes of Health.

FERTILITY--The current decline in fertility in many countries is due to sharply lower fertility rates at the older childbearing ages (over 25), according to the National Institutes of Health.

COLITIS--Ulcerative colitis is a progressive, inflammatory disease of the colon, or large bowel. Affected persons may suffer from cramps, repeated bloody diarrhea, weight loss, anemia, and potentially fatal loss of body fluids and minerals, according to the National Institutes of Health.

Photo Feature

Update...

GIRL RECOVERS
FROM BURNS

One year after the accident that resulted in burns over 92 percent of her body, Sherry White continues her slow, but steady recovery. Much of the medical care she has received at the Parkland Memorial Hospital Pediatric Burn Unit, Dallas, was part of research projects supported by the National Institute of General Medical Sciences and the National Heart and Lung Institute. (See NFFN, September 10, 1973.)

Most patients who are burned over 50 percent of their bodies have died, according to Sherry's physicians Charles Baxter, M.D., and William Curreri, M.D., of the University of Texas Southwestern Medical School Department of Surgery. One of the main reasons for Sherry's survival was the use of the new Dallas Skin Bank, a repository for human skin kept viable by freezing and a research center for developing new techniques.

Above, Sherry wears a type of "wet suit" under her bikini to protect her still delicate skin as she swims with her brother and a friend. At right, Sherry after her May 10, 1973 accident. (NIH Photos #1238, 1121)





Photo Feature

DRS REVISES NIH
RODENT CATALOG

The Veterinary Resources Branch (VRB) of the NIH Division of Research Services maintains nearly 130 different strains and stocks of common and exotic species of rodents and rabbits in its Laboratory Animal Genetic Center.

These animals are used for NIH intramural research and as breeding nuclei for establishing new colonies for extramural use since many of these animals are unique to the VRB. Some endangered stocks have been added to this collection for future biomedical research.

A newly revised "Catalog of NIH Rodents" which describes and indexes the characteristics of the strains and stocks maintained in the NIH Laboratory Animal Genetic Center will soon be available. The descriptions include the frequency and age of appearance of spontaneous tumors, growth of transplantable tumor lines, resistance and susceptibility to infectious agents, behavioral characteristics, blood pressure levels, biochemical and physiological characteristics, and unique anatomical features.

Carl T. Hansen, Ph.D., a geneticist in the Small Animal Resources Section of the Veterinary Resources Branch, refers to his collection as a "living library" of animal models. The Section is headed by Francis Judge, D.V.M.; Robert A. Whitney, Jr., D.V.M., is the Chief of the Veterinary Resources Branch.



*Guy Linthicum, who has been caring for hamsters and rats for 27 years, weighs a hamster as a fellow hamster looks on to verify the results.
(NIH Photo #1239)*

(more)

Rodent Catalog (Cont'd)



The Division of Research Services maintains a broad collection of animal models in its Veterinary Resources Branch. The branch refines and improves available models as well as develops models for the study of such diseases as PKU, cystic fibrosis, diabetes mellitus, and hypertension. Other work involves problems of aging and certain ophthalmology research. Shown are a white rat (upper left), a mouse checking its family tree, two rabbits who are close friends, and a guinea pig being cared for by Rosie Lee Ingram. (NIH Photos #1240, 1241, 1242, 1243)



Medical News Tip

AGING AND STRESS--Older persons suffer increased stress when forced into a new living situation.

Investigators supported by the National Institute of Child Health and Human Development have found that a group of older people who were forced to relocate because of urban renewal, increases in rent, or because their homes were condemned for health reasons, suffered increased morbidity and mortality.

In addition, examination of individuals anticipating relocation showed elevated blood pressure. Blood tests indicated either a reduced food intake to the point of near starvation or exhaustion of the adrenal gland, the organ important in helping the body respond to stress. When compared with old people not facing relocation, the study group had far more hospitalizations for physical illness and psychiatric depressions, as well as a higher mortality rate.

For additional information, contact:

NICHD
Room A-804, Landow Bldg.
Bethesda, MD 20014
Phone: (301) 496-5133

#



New Publication:*What Are the Facts About Genetic Disease?*

Diseases involving disorders of the genes and chromosomes are the oldest, most widespread, and probably the most burdensome of all human afflictions. Some victims of genetic diseases are born with the condition; others are born with the susceptibility to develop the disease in later life.

Genetic diseases are transmitted in essentially three forms: as chromosomal abnormalities, as single-gene defects, and as complex disorders resulting from the combined action of multiple genes and/or environmental factors.

The recognition of specific gene defects in a growing number of conditions has given medical science the capability to identify carriers of the trait and to counsel prospective trait-carrying parents on their risk of bearing a defective infant. Genetic counseling has become an important medical service for families who risk the transmission of serious hereditary disorders. The counselor helps the family choose the course of action which seems appropriate to them in view of their risk, their family goals, and their ethical and religious standards.

A new publication, *What Are the Facts About Genetic Disease?*, has been distributed by the National Institute of General Medical Sciences as part of the announcement of two new human genetics centers. One center at the University of Pennsylvania, Philadelphia, is headed by William J. Mellman, M.D. The other, directed by Walter E. Nance, M.D., is at the Indiana University Medical Center, Indianapolis.

News Releases Issued

CANCER-CAUSING CHEMICALS--The National Cancer Institute (NCI) has awarded a \$6.6 million contract to Tracor Jitco, Inc. to manage the NCI testing program to identify cancer-causing chemicals and physical agents in the environment. This 15-month contract is the second largest ever awarded by NCI and it is the first in which a large portion of a research program will be managed by a non-Federal institution. Scientists estimate that of several hundred thousand chemicals present in the environment, humans receive major exposure to about 20,000. It is believed that environmental factors may be associated with more than two-thirds of the human cancers.

RADIATION TREATMENT--NCI has announced a \$1.5 million grant to the American College of Radiology to evaluate existing methods of radiation treatment for cancer and to establish radiation treatment. Dr. Simon Kramer of the Thomas Jefferson University Hospital, Philadelphia, will direct the three-year project for NCI and the Commission on Radiation Therapy of the American College of Radiology. A group of 24 radiation therapists, 50 radiotherapy residents, and 10 clinical physicists are being recruited to carry out the study. The use of radiation therapy in the U.S. and Puerto Rico will be documented region by region, and criteria developed for optimal radiation therapy.

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See page 1

RESEARCH ADVANCES:

Page

- Scientists Develop Test for Early Pregnancies.....1
- New Kind of Vaccine Shows Promise Against Influenza.....5
- Digestion of Dietary Fat Begins in Esophagus, Stomach.....8

NEWS & PHOTO FEATURES:

- Spinal Cord Centers Work to Reverse Injuries.....9
- Alligator Tongue Oil Relieves "The Miseries".....12

MEDICAL NEWS TIP:

- Aging After the Menopause.....13

NEW PUBLICATION:

- Chronic Obstructive Lung Diseases*.....14

NEWS RELEASES ISSUED:

- Acupuncture.....15

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Research Advances

In Macaques and Baboons...

SCIENTISTS DEVELOP TEST FOR EARLY PREGNANCIES

A new diagnostic test permits the rapid identification of early pregnancies in macaques and baboons. The test thereby extends the investigational use of these primates when the earliest possible diagnosis of pregnancy is desired.

The test, developed by Gary Hodgen, Ph.D., and Griff Ross, M.D., Ph.D., of the Reproduction Research Branch, National Institute of Child Health and Human Development (NICHD), depends on the presence of chorionic gonadotropin, a pregnancy hormone in urine.

Previously, detection of the hormone in urine of monkeys and baboons involved an expensive, time-consuming biologic assay and required collection of a 24-hour specimen.

This discovery enhances the usefulness of these primates in the study of the teratogenic effects (physical defects in the developing embryo) of infectious diseases or drugs, since the developing fetus may be vulnerable to such external factors only during very early pregnancy. Also, an early definitive test result is vital in the

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Technician Donald Barber collects urine from the bottom of a monkey's cage to be used to diagnose pregnancy in the animal. (NIH Photo #1244)

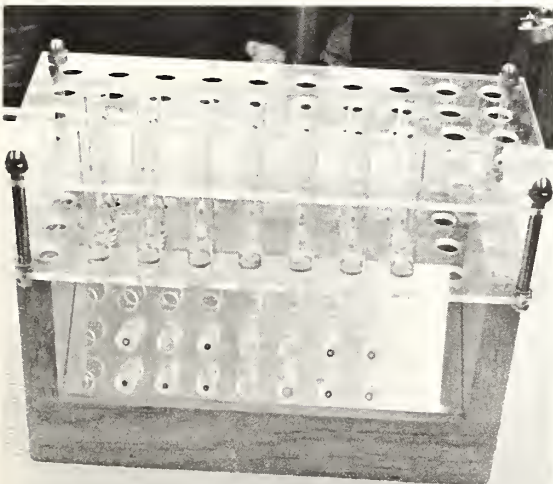
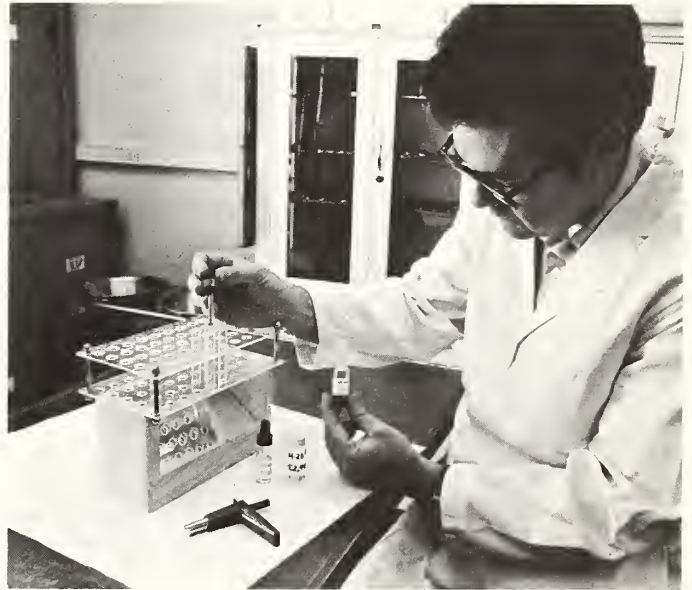
Pregnancies (Cont'd)

evaluation of most types of fertility control. From the results of such studies, scientists can draw inferences about how these agents may affect fertility or fetal growth and development in man.

The new test is particularly timely due to the restrictions on the importing of primates, especially rhesus monkeys, for research. Since the shortage has necessitated large scale domestic breeding of this primate (which is used extensively in biomedical research), the new diagnostic test will facilitate maximum breeding efficiency by

(more)

To begin the test, technician Charles Turner adds antiserum to the urine specimens. After two hours, the technicians will check the results. (NIH Photo #1245)



Both test tubes must show dark circles for the results to be positive. Results shown above are (from left): positive, negative, positive, inconclusive, negative, positive, positive. (NIH Photo #1246)

Pregnancies (Cont'd)

early differentiation between females which have conceived during the past menstrual cycle and those requiring remating.

The new test procedure was developed using an antiserum (developed by the scientists) to the beta subunit of ovine luteinizing hormone. The antiserum reacts with antigenic determinants common to the chorionic gonadotropins of humans, gorillas, orangutans, chimpanzees, baboons, and macaques, but not to follicle stimulating hormone or luteinizing hormone of the latter two species. The presence of macaque or baboon chorionic gonadotropin inhibits the agglutination of human chorionic gonadotropin-coated ovine erythrocytes.

The hemagglutination inhibition test is rapid, simple, and inexpensive and gives the investigator a definitive diagnosis of pregnancy by the 18th day after fertilization. This is up to three weeks earlier than conventional pregnancy diagnosis by palpation and is vastly superior to bioassays which are less sensitive, more time-consuming, and expensive.

The new test, which requires two hours and only 200 microliters of urine, is reliable in that the frequency of false negative or false positive results is less than one percent.

The antiserum has also been used to develop a highly sensitive and specific radioimmunoassay for chorionic gonadotropin in these primates. This more sensitive, quantitative method has been used to detect chorionic gonadotropin in serum and urine as early as nine days after fertilization, which is coincident with implantation. However, the radioimmunoassay is not now practical for routine pregnancy diagnosis.

A report of the new hemagglutination inhibition test procedure appears

(more)

Pregnancies (Cont'd)

in the May, 1974 issue of *The Journal of Clinical Endocrinology and Metabolism*.

Sufficient antiserum is available for over five million pregnancy tests. Kits containing reagents for the diagnostic test are being prepared under a contract administered by the Contraceptive Development Branch of the Center for Population Research, NICHD. By the end of the year, kits will be available by application to the Hormone Distribution Officer, Office of the Director, National Institute of Arthritis, Metabolism, and Digestive Diseases, Building 31, Room 9A-47, Bethesda, MD 20014.

#



Dr. Hodgen checks the results of the new pregnancy detection test (NIH Photo #1247)

Research Advances

NEW KIND OF VACCINE SHOWS
PROMISE AGAINST INFLUENZA

The principle of "divide and conquer" has been successfully applied by medical researchers in their attempts to overcome the influenza virus.

In animal studies and clinical trials, scientists supported by the National Institute of Allergy and Infectious Diseases (NIAID) have demonstrated that a vaccine aimed at only one component of an influenza virus can prevent illness by and induce resistance to non-identical but antigenically similar influenza viruses. This observation is particularly important in dealing with the influenza A virus which is known to "drift" antigenically almost every year and to "shift" dramatically about every 10 years.

This new kind of vaccine--tried first in mice--was tested recently in volunteers in Texas by a team of investigators headed by Robert B. Couch, M.D., of Baylor University College of Medicine, Houston. The vaccine's development is based on basic research findings reported over the years on the structure and function of various components of the influenza A virus. Scientists now know, for example, that the outer coat of the influenza virus is studded with molecules of two proteins, known as hemagglutinin (H) and neuraminidase (N), which act as antigens. These proteins, in fact, are used by scientists as code names for different strains of the virus, such as H3N1 or H1N2.

It is also known that, during the last 40 years, there have been only two neuraminidase subtypes defined in human influenza virus. During the same period, the hemagglutinin has changed four times. For this reason, Edwin D. Kilbourne, M.D., and associates at Mt. Sinai School of Medicine, New York,

(more)

Influenza Vaccine (Cont'd)

theorized that it would be easier to induce immunity to the less variable neuraminidase enzyme than to chase the more shifty hemagglutinin.

The vaccine used in the present clinical trial was a "tailor-made" hybrid prepared from the hemagglutinin (H eq 1) of a horse influenza virus and the neuraminidase (N2) of a human influenza virus. The end result was H eq 1 N2, or X-32, as it was referred to in the test. Because the H eq 1 is an irrelevant hemagglutinin, non-cross-reactive with human influenza viruses, the investigators could be sure that only immunity to the N2 component would be induced in volunteers receiving the X-32 vaccine. Controls in the study were given a completely irrelevant influenza B virus vaccine.

Thirty-nine volunteers participated in the study. Since six of these were found to have preexisting antibodies to N2, they were automatically given X-32. The other 33 men were assigned, randomly, to receive either X-32 or influenza B vaccine. Five weeks later, each of these 33 subjects was given the same vaccine he originally received. The volunteers who had had antibody to N2 prior to vaccination were given only a saline solution as a simulated booster dose since, as far as antineuraminidase activity was concerned, their initial dose of X-32 had served as a booster.

Nine days after the second vaccination, all men were challenged with live Hong Kong flu virus (H3N2); six months later all volunteers still in the study were challenged a second time.

The scientists found that the incidence of infection--as evidenced by a rise in antibody--was about the same in both control and vaccinated groups, but the incidence of illness in volunteers who had received X-32 was very

(more)

Influenza Vaccine (Cont'd)

much reduced. Furthermore, rechallenge of volunteers demonstrated complete protection of men vaccinated with X-32 who had been infected during the first challenge.

The NIAID-supported investigators, on the basis of their experiments, conclude that availability of a monospecific influenza vaccine, such as X-32, might improve efforts to prevent the disease. Present recommendations call for yearly immunization with a vaccine made from the currently prevalent influenza virus. In contrast, vaccination monospecific for the neuraminidase enzyme could allow infection without illness to take place under natural conditions and thus might allow for more potent and durable immunity to be achieved. Another possible use of neuraminidase-specific immunization might be in combination with a live vaccine since the damping effect of anti-neuraminidase antibody would reduce the need for and time required for full attenuation of the live virus.

This work was reported in the April 1974 issue of the *Journal of Infectious Diseases* by Dr. Couch and Julius A. Kasel, Ph.D., of Baylor; John L. Gerin, Ph.D., Molecular Anatomy Program, Rockville Laboratory, Oak Ridge National Laboratory; and Jerome L. Schulman, M.D., and Dr. Kilbourne, Mt. Sinai School of Medicine, City University of New York.

Research Advances
Brief Report

DIGESTION OF DIETARY FAT
BEGINS IN ESOPHAGUS, STOMACH

Digestion of dietary fat starts in the esophagus and in the stomach, not in the uppermost part of the intestine (duodenum) as previously believed.

This report comes from Margit Hamosh, Ph.D., Robert O. Scow, M.D., and Hayden Klaeverman, M.D., of the National Institute of Arthritis, Metabolism, and Digestive Diseases and by Robert O. Wolf, D.D.S., of the National Institute of Dental Research. The researchers report that the breakdown of the fat is started through the action of an enzyme released from the throat.

Drs. Hamosh and Scow described the new enzyme--called pharyngeal lipase and thought to be secreted by the tongue of rats--in January 1973. However, they now have evidence that the enzyme is also secreted in humans and that it initiates digestion of dietary fat in the stomach.

Several diseases involved the inability to digest fat properly, notably conditions recurring in premature infants. Additionally, atherosclerosis is characterized by fatty deposits in blood vessels. However, the NIH scientists described as speculative at this time any effort to point to possible applications of their research findings.

The investigators presented their findings at the meeting of the American Federation for Clinical Research, May 5, 1974.

Photo Feature

SPINAL CORD CENTERS
WORK TO REVERSE INJURIES

At the five Acute Spinal Cord Injury Clinical Research Centers, work is directed toward analyzing the causes, complications, and treatments of spinal cord injuries in an effort to minimize or reverse this damage.

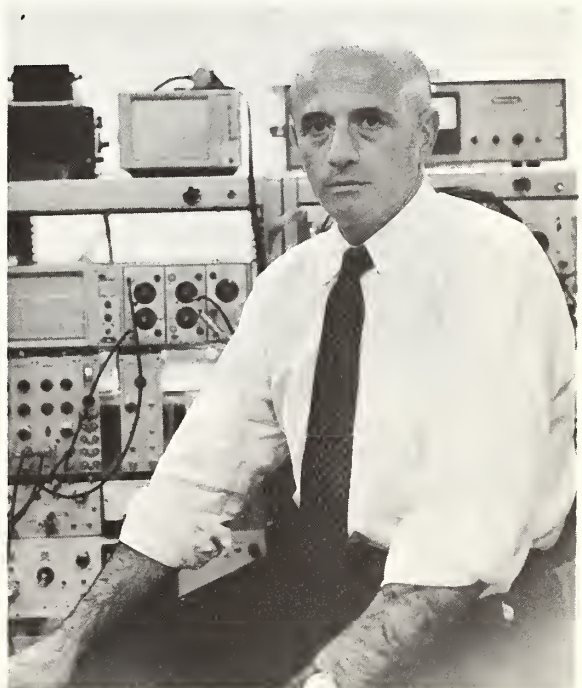
The program, supported and administered by the National Institute of Neurological Diseases and Stroke, involves the St. Joseph's Hospital and Medical Center, Phoenix, Arizona; the Medical University of South Carolina at Charleston; New York University, New York City; Ohio State University, Columbus; and Yale University, New Haven, Connecticut.

Past treatments of spinal cord injuries offered little hope of improvement. However, recent studies of nerve damage have indicated the possibility of stopping or reversing the progressive nerve damage that starts soon after a severe spinal injury. The use of hypothermia as well as the use of steroids and other drugs that may inhibit the pathological process that destroys spinal cord tissue after injury has also been promising.

Annually in this country, 5,000 to 10,000 new cases of spinal cord injuries--particularly in young adult males--are caused by accidents.

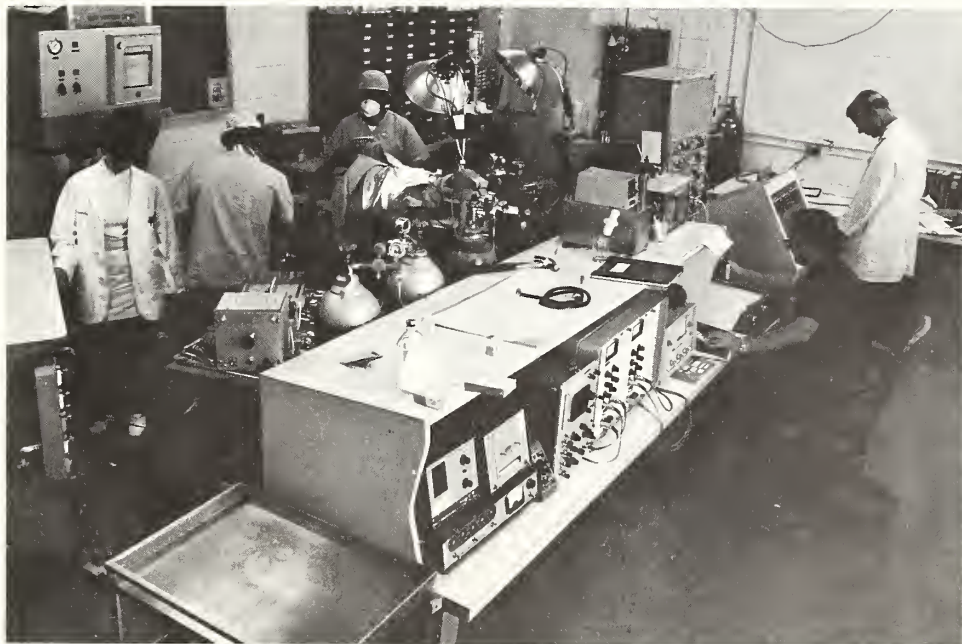
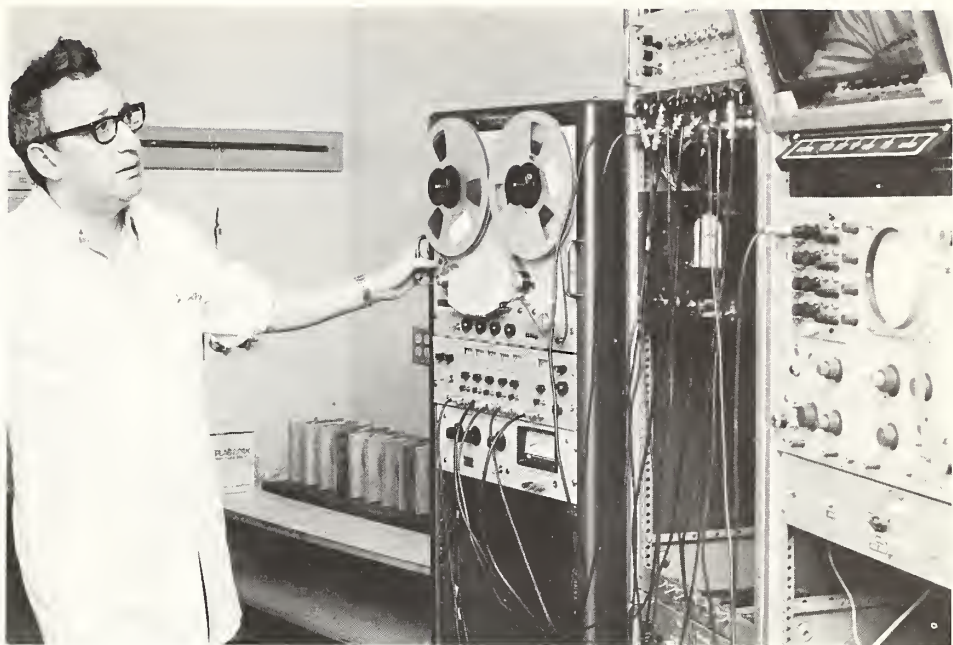
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Edward R. Perl, M.D., University of North Carolina, heads the Spinal Cord Injury program project. (NIH Photo #1248)



Spinal Cord (Cont'd)

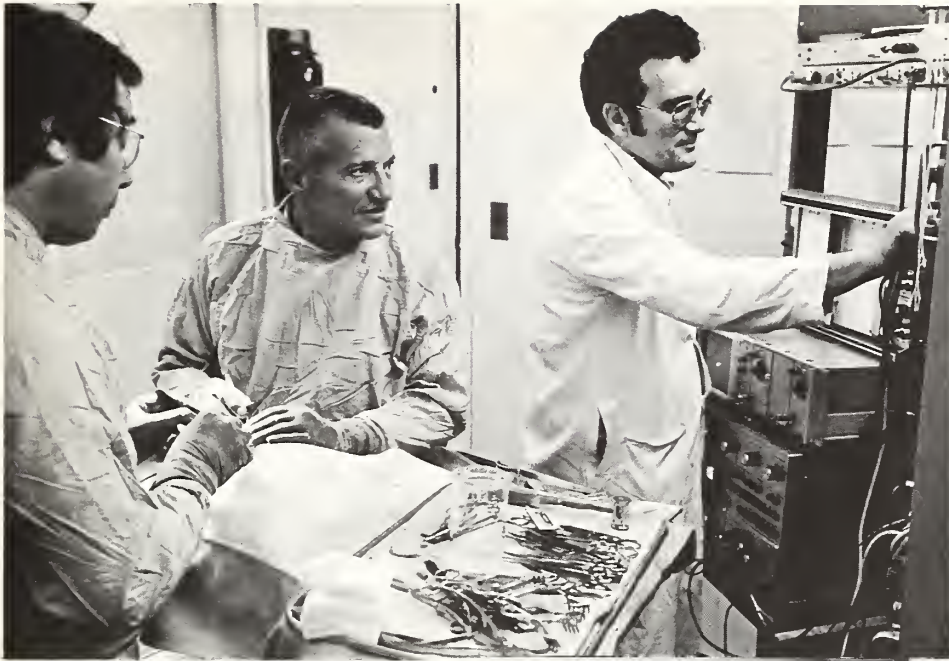
Eduardo Eidelberg, M.D., principal investigator of the Spinal Cord Injury Center at the Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, demonstrates the apparatus which shows how much functional conduction remains in the spinal cord of a lab animal after injury. (NIH Photo #1249)



At the Medical University of South Carolina, Charleston, researchers study in animals how the spinal cord injury develops and how, through the application of drugs and other experimental procedures, the resulting paralysis or nerve damage can be prevented or modified. Phanor L. Perot, Jr., M.D., is principal investigator for the Spinal Cord Center. He is professor and chairman of the University's Division of Neurosurgery. (NIH Photo #1250)

(more)

Spinal Cord (Cont'd)



At the New York University School of Medicine Spinal Cord Center (above), Eugene Flam, M.D., (left) and Joseph Ransohoff, M.D., (center) record the evoked potential of the spinal cord following impaction injury to an animal model. Dr. Flam, assistant professor of neurosurgery, and Dr. Ransohoff, professor and chairman of the department, are assisted by research scientist John Tonasula. (NIH Photo #1251)



At the Ohio State University Spinal Cord Center, William E. Hunt, M.D., (right) and Joseph Goodman, M.D., check the apparatus used to induce spinal cord injuries in animals. The investigators study the animals during the important first four hours after the onset of injury. (NIH Photo #1252)



William F. Collins, M.D., (left photo) is principal investigator at the Spinal Cord Injury Center at Yale University. (NIH Photo #1253)

Photo Feature

ALLIGATOR TONGUE OIL
RELIEVES "THE MISERIES"

The Louisiana bayou country folk have been taking alligator tongue oil orally for more than 100 years to relieve "the miseries." Paul M. Sacco, Ph.D. (left), and Allen B. Staton, pharmacology researchers at Xavier University of Louisiana, New Orleans, are studying alligators in order to delve into the mysteries of this old Cajun folk medicine. The researchers, working with the Minority Biomedical Support (MBS) program of NIH's Division of Research Resources (DRR) have determined that the alligator tongue oil has certain chemical derivatives which produce a steroidal action in the body. The consumption of the oil causes profuse perspiration and is claimed to give temporary relief from asthma, rheumatism, and arthritis. A report of these findings was made at the Second Annual Xavier-MBS Biomedical Symposium held in New Orleans, April 1974. The symposium, attended by scientists from predominantly ethnic minority colleges and universities, was co-sponsored by Xavier and DRR. (NIH Photo #1254)

Medical News Tip

AGING AFTER THE MENOPAUSE--Studies supported by the National Institute of Child Health and Human Development (NICHD) have shown that in addition to the estrogen produced by the ovaries of women during their reproductive years, there is another biologically less active form of estrogen produced by other tissues of the body. According to recent findings, this "extra-ovarian" source of estrogen continues and may even increase after the menopause.

Investigators have also found that after the menopause conditions such as liver disease and obesity increase production of this estrogen.

Such studies will provide a better understanding of these extra sources of estrogen and may help to explain why women differ in menopausal symptoms and why some women have a greater need for replacement therapy than others.

For additional information, contact:

NICHD
Room A-804, Landow Bldg.
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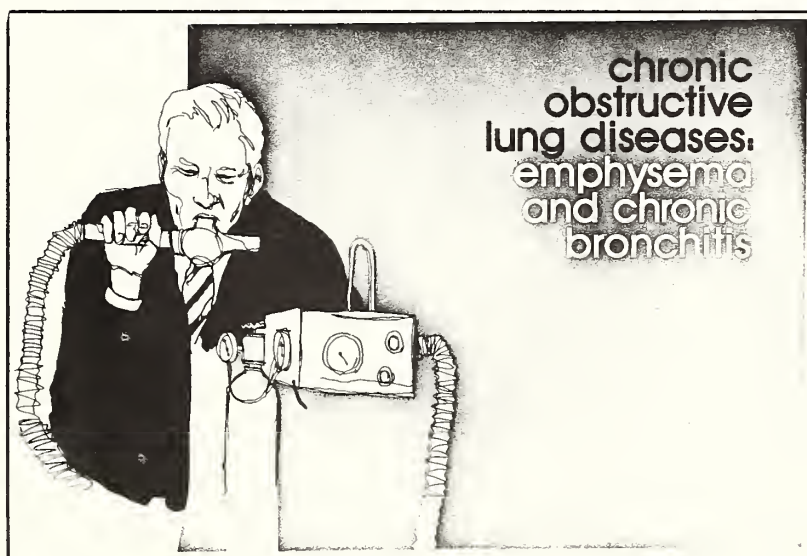
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New Publication:*Chronic Obstructive Lung Diseases*

The National Heart and Lung Institute (NHLI) has released a new publication, *Chronic Obstructive Lung Diseases: Emphysema and Chronic Bronchitis*. This new booklet contrasts normal breathing with the breathing of a patient with chronic bronchitis or emphysema.

The principal cause of chronic bronchitis is prolonged irritation of the bronchial tube linings. Smoking, air pollution, and recurrent respiratory infections are the main irritants, causing the mucus glands and cells to overproduce and the sensitive membrane to thicken, swell, and become obstructed. This, in turn, promotes the development of the companion disorder, emphysema.

Of the estimated 1.3 million Americans who have emphysema, more than half are younger than age 65. In terms of disability costs, emphysema ranks third among all diseases, exceeded only by heart and mental disorders.



Science writers can obtain a free copy of this new publication from:
NHLI, National Institutes of Health, Building 31, Room 5A-21, Bethesda,
MD 20014.

News Releases Issued

ACUPUNCTURE--The National Institute of General Medical Sciences has awarded two grants for new research studies to assess the pain-relieving capabilities of acupuncture. One project, to be conducted by Yung-Fong Sung, M.D., at Emory University, will attempt to determine a neurophysiological basis for acupuncture anesthesia. Dr. Sung will also compare the effects of acupuncture to narcotic analgesics in the treatment of postoperative pain experienced by patients following tonsillectomies or multiple tooth extractions. At the University of North Carolina, Chapel Hill, Edward R. Perl, M.D., will test the ability of acupuncture to alter the sensation of touch and the sensations of heat and vibration as perceived through the skin.

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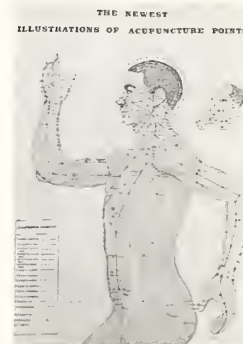
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See page 12

	<u>Page</u>
RESEARCH ADVANCES:	
Immunosuppressive Drugs May Reactivate EB Virus.....	1
Scientists Find Unusual Bacteria.....	4
Transformed Cells Produce Antibody in Continuous Culture.....	6
NEWS & PHOTO FEATURES:	
Doctors Will "See" Patients Via New Satellite.....	8
NICHD Seeks to Reduce Perinatal Mortality.....	11
Dental Acupuncture Decreases Sensitivity to Pain.....	12
MEDICAL NEWS TIP:	
Advancing Age and the Immune System.....	14
NEW PUBLICATION:	
<i>Cost Analysis & Rate Setting Manual</i>	15
NEWS RELEASES ISSUED:	
Venereal Disease.....	16

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Research Advances

IMMUNOSUPPRESSIVE DRUGS
MAY REACTIVATE EB VIRUS

Excretion of Epstein-Barr (EB) virus is three times more common in kidney transplant and other immunosuppressed patients than in untreated individuals. According to NIH-supported investigators at the Yale University School of Medicine, this finding supports the hypothesis that immunosuppressive drugs reactivate latent EB virus infections.

Previous studies have established that patients with infectious mononucleosis shed the EB virus for many months after the acute illness. (See *NFFN*, March 25, 1973.) In the present study, investigators Barry Strauch, M.D., Norman Siegel, M.D., Linda-Lea Andrews, and George Miller, M.D., attempted to determine if this was also true of renal transplant and other immunosuppressed patients. Such information might throw light on natural defense mechanisms which terminate the viral carrier state.

Immunosuppressive drugs are used when it is necessary to overcome the body's immune mechanisms, such as in organ transplantation. These agents are also used to treat autoimmune diseases in which the body, for reasons still unknown, begins to destroy its own cells or organs. Patients on these drugs become susceptible to many infections, particularly by the herpes group of viruses. (EB virus is characterized as "herpes-like.")

Epstein-Barr virus is regularly associated with not only infectious mononucleosis but also with some forms of cancer, particularly Burkitt's lymphoma, a tumor usually found in the jaw or facial bones of children in central Africa. The virus has been found to induce in the marmoset a disease resembling reticulum cell sarcoma--a malignancy occurring frequently in

(more)

EB Virus (Cont'd)

renal transplant patients.

The most significant biologic property of the EB virus is its ability to transform normal human lymphoid cells into continuously proliferating *in vitro* cell lines. The Yale investigators employed this property when they measured virus shedding in 80 study patients and staff in a hospital-based renal-disease unit. The four groups of individuals tested included patients with kidney transplants, patients treated with immunosuppressive drugs, patients with chronic uremia, and healthy staff members associated with the unit.

The investigators obtained specimens by throat washings, inoculated these onto cultures of mixed lymphocytes, and then examined these for transformation.

As a result, they found that 20 of the 25 cell lines that converted were positive for EB virus. Seventy-five percent of these had been inoculated with specimens from immunosuppressed patients.

During the course of the study, five additional patients--none of whom was a virus shedder--received kidney transplants. After the transplant and initiation of immunosuppressive drug treatment, two patients became EB virus shedders.

The Yale scientists suggest that it was a latent, endogenous EB virus which was reactivated. They also suggest that virus shedding in immunosuppressed patients involves cell-mediated immune mechanisms rather than humoral ones, since the shedding occurred in the presence of circulating antibody.

(more)

EB Virus (Cont'd)

The investigators published a full report of these findings in the February 16, 1974 issue of *Lancet*. The work was supported by grants from the National Institute of Allergy and Infectious Diseases, the National Cancer Institute, and NIH's Division of Research Resources.

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CANCER CONTROL--The Cancer Control Program helps ensure that existing knowledge of cancer detection, diagnosis, treatment, and rehabilitation will be disseminated and applied as rapidly and effectively as possible, according to the National Institutes of Health.

NEUROMUSCULAR DISORDERS--The two most common neuromuscular disorders are the muscular dystrophies and myasthenia gravis. According to the National Institutes of Health, these disorders afflict approximately 200,000 and 30,000 patients respectively.

Research Advances

In Decayed Tooth Roots...

SCIENTISTS FIND UNUSUAL BACTERIA

Grantees of the National Institute of Dental Research have found unusual bacteria not seen in decay of tooth crowns deep in human tooth roots.

David L. Sumney, D.M.D., and Harold V. Jordan, Ph.D., report that decay in human tooth roots starts by the gradual penetration of cementum, the cover of teeth below the gum line. They note that many of the bacteria which make plaque in this region are the same as those found in plaque on tooth crowns, including *Streptococcus mutans*. Tooth destruction continues by bacterial penetration into the tubules of the dentin which comprises the body of teeth. Decay then spreads sideways between the tubules to form irregular soft spots.

Deeper in the dentin, the scientists find sparse, rod-shaped bacteria called *Arthrobacter* invading the tubules as pioneers of decay. *Arthrobacter* do not make acid and therefore cannot initiate decay on highly mineralized surfaces such as enamel or cementum. They do metabolize proteins which are more available in tubules than in the mineralized portion of dentin.

Previous research with animals has indicated that components of bacterial plaque are not the same in different locations. Therefore, the scientists designed their study to learn whether bacteria in humans also vary with the location of the plaque. Of the surface organisms on roots, they found that a sizeable group of round forms (21 strains) belonged to the *Streptococcus mutans* family, and a smaller group were alpha hemolytic types of *S. sanguis*. Fifteen more were *S. mitis* strains (also alpha hemolytic), and 18 others had characteristics of the enterococci, bacteria usually found in the intestinal

(more)

Bacteria (Cont'd)

tract. Another sizeable group of round forms (27 strains) were kin to the staphylococci and micrococci, and a small group were identified as *Neisseria sicca*.

Of the thread-like forms, fifteen strains were *Actinomyces*, a group which is known to cause root decay in animals, and has also been associated with periodontal inflammation.

However, the pioneer rods deep in the root tubules were diphtheroids that were Gram positive, grew well on a medium selective for lactobacilli, and required oxygen. Although they do not ferment glucose, they do extract nourishment from proteins so could cause damage as secondary invaders of dentin. The investigators say that these bacteria fit best into the genus *Arthrobacter* whose members are usually found in soil or salt water.

This research suggests that root decay may progress in two stages. Acids from several kinds of bacteria which ferment sugars or starches apparently make the first breach in the cementum. When that passage is open, a second group of proteolytic organisms may then invade the dentinal tubules.

These findings were reported in the *Journal of Dental Research*, Part 2, March-April 1974. Dr. Sumney, now at the University of Pittsburgh, conducted the study while at the Harvard School of Dental Medicine. Dr. Jordan is at the Forsyth Dental Center.

Research Advances

TRANSFORMED CELLS PRODUCE
ANTIBODY IN CONTINUOUS CULTURE

A group of NIH-supported scientists have succeeded in developing a line of cells capable of growing in culture indefinitely and producing antibody to a pre-selected antigen. Cell lines of this type could prove immensely helpful to researchers in the field of immunology, as well as to physicians needing pure antibodies for therapeutic purposes.

The scientists at Harvard Medical School and the Massachusetts General Hospital started with spleen cells from a rabbit which, following a heavy schedule of immunization, was manufacturing very large quantities of antibody to type S3 pneumococcal polysaccharide. They suspended the cells in nutrient medium, exposed them to the tumor-inducing virus, SV-40, and placed them in 12 different culture dishes. After more than three months of observation, a cluster of transformed (tumor-like) cells was seen on the surface of one culture, and these were used in the remainder of the work.

Using radioactive labels and refined methods of analysis, the investigators found evidence that the transformed rabbit spleen cells produced a single type of anti-S3 antibody--one of four types originally found in the rabbit's serum.

Although, in this study, the amount of antibody produced per transformed cell was small, the investigators' success in establishing a specific antibody-producing cell line in continuous culture is of great interest. In contrast to cultures of antibody-producing cells from spontaneously occurring tumors such as multiple myeloma, the present system may enable researchers to obtain, in quantity, antibodies of predetermined specificity. Such anti-

(more)

Cells (Cont'd)

bodies might be extremely useful both as research tools and as weapons against disease.

A.D. Strosberg, J.J. Collins, P.H. Black, D. Malamud, S. Wilbert, K.J. Bloch, and E. Haber reported their work in the February 1974 issue of the *Proceedings of the National Academy of Sciences*. The scientists were supported, in part, by grants from the National Institute of Allergy and Infectious Diseases, the National Institute of Arthritis, Metabolism, and Digestive Diseases, the National Cancer Institute, and the National Institute of General Medical Sciences.

#

PARKINSON'S DISEASE--Parkinson's disease is a progressive neurological disorder affecting the brain centers responsible for control and regulation of movement, according to the National Institutes of Health. Most frequently attacking people in their fifties and sixties, the disease is thought to be increasing in prevalence with the increase in average lifespan.

Photo Feature

NLM Space Project...

DOCTORS WILL "SEE" ALASKAN
PATIENTS VIA NEW SATELLITE

The National Library of Medicine (NLM) will use NASA's newest communications satellite, the ATS-6, in experiments to extend physician services and medical education in Alaska and the State of Washington. The NLM's Lister Hill National Center for Biomedical Communications, working with HEW's Health Services Administration (HSA) and Health Resources Administration (HRA), will coordinate the experiments.

The Applications Technology Satellite (ATS-6), which was launched from the Kennedy Space Center on May 30, is the most versatile and powerful communications satellite ever developed.

The communications network being developed by NLM will bring physicians into regular visual contact with the remote Alaskan villages of Galena (pop. 425) and Fort Yukon (pop. 630) for the first time. Using the satellite's capability for transmitting high-quality television, physicians at the Indian Health Service hospital in Tanana and medical specialists in Anchorage will be

(more)

Earl Henderson (left), NLM, talks about the ATS-6 satellite with Mrs. Lillie McGarvey, head of Alaska Area Native Health Board, and Martha Wilson, M.D., director, Office of Program Development, Alaska Area Native Health Service. (NIH Photo #1255)



Satellite (Cont'd)

At the ATS-6 launch site are Ernest W. Hartung, M.D. (left), president, University of Idaho; Mr. Henderson; Roy Schwarz, M.D., associate dean, University of Washington School of Medicine; and Marian Johnson, WAMI project officer.
(NIH Photo #1256)



able to "see" patients at the two villages and will be able to prescribe treatment and follow the patients' progress.

NLM is also utilizing the satellite to improve medical education in the Washington-Alaska-Montana-Idaho (WAMI) region. The University of Washington School of Medicine, Seattle, will share its teaching resources with first-year medical students in Fairbanks, Alaska, and with third and fourth-year students at Omak, in central Washington.

Representing NLM at the launch site were Melvin S. Day, deputy director, and Earl Henderson, chief of the Lister Hill Center Communications Engineering Branch.

Although it is not exactly a household term, NLM's Lister Hill National Center for Biomedical Communications is having a direct effect on the lives of many Americans, including New Englanders, Alaskan natives, and the elderly residents of a public housing project in New York's East Harlem. In each case, the key to the Center's involvement is to apply modern technology to improve biomedical communication. The staff of the Center turned to satellites

(more)

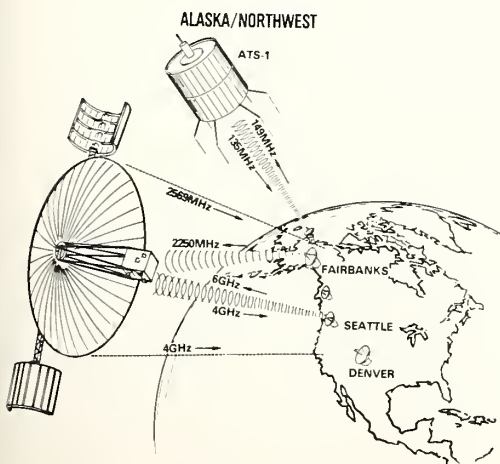
Satellite (Cont'd)

as a means of helping health professionals bridge great distances.

Working with, and coordinating the efforts of the HSA and the HRA, the Center set up in Summer, 1971, a reliable voice communications link, via ATS-1 satellite, to connect physicians at the hospital in Tanana with the health aides in 26 outlying native villages. The experience gained with this network has provided a solid basis for the expanded experiments to be tried via ATS-6.

The existing audio network has been credited with saving lives in several medical emergencies, such as severe burns from a stove explosion and, in a separate case, serious complications during childbirth. The satellite communications network made possible immediate step-by-step first-aid data for the village health aide followed by prompt air evacuation for the patient.

"More important in the long run than these spectacular successes," according to NLM Director Martin M. Cummings, M.D., "is the dramatic increase in the number of patients treated with the advice of a physician in those villages where the satellite radio has been installed. This consultation will be even more effective when the physician can actually see the patient via high-quality television transmitted by the ATS-6 satellite."



Drawing shows relationship of two satellites to Northwestern states. In photo, Mr. Henderson (left) at the ATS-6 launch site with Melvin S. Day, NLM deputy director. (NIH Photos # 1257, 1258)

#



Photo Feature

NICHD SEEKS TO REDUCE
PERINATAL MORTALITY

The greatest number of perinatal deaths occur during the last 24 hours before birth and the first 24 hours of life. Alterations in the normal processes of labor and birth, along with the inability of the newborn to adapt to extrauterine life present the greatest threats to survival during this period.

Most babies who fail to survive their first full day die because of immaturity and respiratory insufficiency. The National Institute of Child Health and Human Development (NICHD) supports research on such national health problems as part of the Perinatal Biology and Infant Mortality Branch. The branch coordinates a program of research and training to increase knowledge concerning pregnancy and maternal health, embryonic development, fetal growth, and infant well being through the first year of life.

According to Eileen G. Hasselmeyer, Ph.D., R.N., branch chief, "One of our priorities is to eradicate those maternal, fetal, and infant health problems which result in the highest incidence of infant morbidity and mortality."



To assure an infant's survival and well being during the crucial perinatal period, doctors check the heart beat one minute after birth. (NIH Photo #1259)

Photo Feature

DENTAL ACUPUNCTURE DECREASES
SENSITIVITY TO PAIN

Richard Chapman, M.D., of the University of Washington, Seattle, uses dental acupuncture to study sensitivity to pain and a person's willingness to call a noxious stimulus painful.

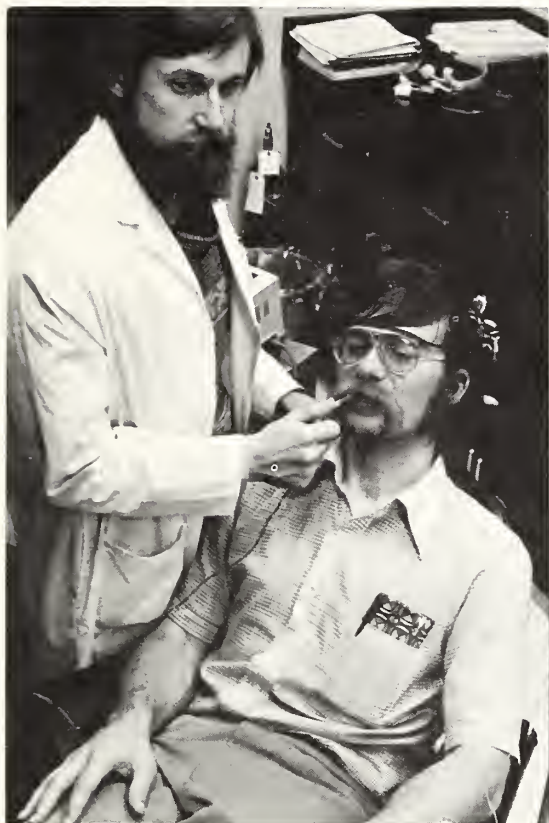
Dr. Chapman has compared the effects of 33 percent nitrous oxide and acupuncture on the perception of pain produced by applying stimulus to the teeth which simulated dental pain. He has found that both nitrous oxide and acupuncture made subjects less willing to acknowledge pain, and that acupuncture, as well as nitrous oxide, significantly decreases the sensitivity to pain. However, acupuncture seems more effective than nitrous oxide, in decreasing the perception of pain stimuli of stronger intensity.

These findings suggest to Dr. Chapman that acupuncture may have effects in addition to the psychologic. The findings also raise many questions concerning the method of action of analgesic drugs, acupuncture, and modifications in behavior and provide a precise clinical research tool for comparing the effectiveness of these different approaches to the control of pain.

Dr. Chapman, who is currently in China studying acupuncture techniques, is supported in his acupuncture studies by the National Institute of General Medical Sciences.

(more)

Acupuncture (Cont'd)



Dr. Chapman applies acupuncture needles to hand points and uses an electrical current device to provide acupuncture anesthesia. Once the needles are applied, he performs dental work on the patient.

NIH Photos #1260 (left) and 1261 (below)



<u>Indications.</u>		<u>Hand Signals.</u>
Nothing:	0	
Possible Sensation:	1	
Pre-pain Sensation:	2	
Very Faint Pain:	3	
Mild Pain:	4	
Moderate Pain:	5	
Strong Pain:	6	

During the dental work, the patient uses hand signals to signify the amount of pain he is experiencing. Dr. Chapman has prepared a chart of appropriate hand signals for differing amounts of pain.

(NIH Photo #1262)

Medical News Tip

ADVANCING AGE AND THE IMMUNE SYSTEM--Advancing age is known to be accompanied by a decline in the immune system. Scientists are investigating many aspects of immunity through studies with populations of aging mice and are beginning to pinpoint where in the system this wearing out process begins.

The major defect is the inability to produce enough cells to respond effectively to challenges. In a recent study, scientists supported by the National Institute of Child Health and Human Development discovered that the inability of the immune system to operate effectively may be due to the presence of a certain type of white blood cell (a repressor) shown to be more common in old than in young mice. The investigators will now attempt to correct the defect in the system by removing the repressors. If this correction can be achieved, it could point the way toward beneficially modifying the immune system in the aged human.

For additional information about research on the immune system and aging, contact:

NICHD
Room A-804, Landow Bldg.
Bethesda, MD 20014
Phone: (301) 496-5133

#



New Publication:*Cost Analysis & Rate Setting Manual*

A 109-page manual, designed to help improve financial management of animal resource facilities, has been produced by the Animal Resources Branch of the Division of Research Resources, National Institutes of Health (NIH), in cooperation with the Association of American Medical Colleges (AAMC).

Cost Analysis and Rate Setting Manual for Animal Resource Facilities is intended to aid laboratory animal facility directors and administrators in establishing realistic charge rates for animal care and related services, and justify them to investigators using the facilities and their sponsoring agencies.

The manual sets forth step-by-step procedure by which institutions can analyze animal care costs. Such an analysis, in addition to being basic to rate setting, can be of value in identifying areas where cost reductions might be instituted. Also, the analysis is an aid in budget formulations and in the general administrative management of an animal resource. The manual discusses methods of using the analysis in all of these areas.

Single copies of the manual can be obtained free from the Animal Resources Branch, Division of Research Resources, National Institutes of Health, Bethesda, MD 20014.

News Releases Issued

VENEREAL DISEASE--The National Institute of Allergy and Infectious Diseases has awarded its first program project grant for venereal disease research to Dr. King K. Holmes, of the University of Washington. Dr. Holmes and his associates will explore three important areas of research: 1) clinical epidemiology and pathological changes leading to gonorrhea; 2) genetics in *Neisseria gonorrhoeae* (the causative organism in gonorrhea); 3) and the causes, clinical manifestations, and treatment of non-gonococcal urethritis. Studies such as those supported by this grant will provide the means to prevent new cases of venereal diseases and to detect and treat those who are infected.

#

SPEECH & HEARING--It is estimated that 10,000,000 Americans have handicapping speech disorders such as stuttering, laryngectomy, and cleft palate; 8,500,000 have hearing impairments; and 2,100,000 have a central communicative disorder such as aphasia and mental retardation, according to the National Institutes of Health.



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June 25, 1974



See page 7

RESEARCH ADVANCES:

Page

Anti-Gout Medication Prevents Familial Mediterranean Fever.....	1
New Selenoprotein May Aid In Muscular Dystrophy Research.....	3
New Test Diagnoses Kidney Infections.....	5

NEWS & PHOTO FEATURES:

Cleft Palate Group Counsels Mothers.....	7
The "Body Box" Increases Pulmonary Disease Detection.....	10
Screening Tests Identify Cystic Fibrosis Carriers.....	11
Eels and Cobra Venom Contribute to Myasthenia Gravis Research.....	13

MEDICAL NEWS TIP:

Infection and Trauma.....	14
---------------------------	----

NEW PUBLICATION:

<i>Dust Allergy</i>	15
---------------------------	----

NEWS RELEASES ISSUED:

Cancer Centers.....	16
---------------------	----

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Research Advances

In Controlled Trials...

ANTI-GOUT MEDICATION PREVENTS
FAMILIAL MEDITERRANEAN FEVER

Attacks of Familial Mediterranean Fever (FMF)--a rare inherited disease--can be prevented by use of the anti-gout drug colchicine, according to National Institute of Allergy and Infectious Diseases (NIAID) scientists.

Although many agents have been considered of value in treating FMF since the discovery of this disease in 1908, the present study by NIAID scientists Sheldon M. Wolff, M.D., and associates is the first controlled trial of any therapy for the disease.

Attacks of Familial Mediterranean Fever are characterized by nausea, extreme pain in the abdomen or chest, prostration, and fever. Because these symptoms are unpredictable and subside of their own accord after a few days, Dr. Wolff and his associates felt it extremely important that their evaluation of colchicine be a controlled, double blind trial.

The scientists randomly assigned courses of colchicine or placebo to 11 patients with long-standing FMF. Nine of these patients were having attacks on the average of at least once per month; the other two were experiencing attacks every six to eight weeks.

Each patient took tablets of placebo or colchicine for a total of 28 days for each course or until an attack occurred. The next course was started when the attack ended. Eight of the patients were treated at the NIH Clinical Center and three received treatment at the Massachusetts General Hospital, Boston.

(more)

FMF (Cont'd)

Dr. Wolff reports that pooled patient data reveal striking results. Of the 60 placebo courses, 38 were terminated by attacks. However, during the same number of colchicine courses, only seven attacks occurred. According to the investigators, these data demonstrate that colchicine, when compared with placebo, significantly reduced the number of FMF attacks.

Since almost all of the patients developed gastrointestinal side effects while taking as many as three tablets of colchicine a day, the investigators reduced the dosage for the majority of the courses. When they analyzed the study data, it could be seen that the effect of colchicine was dose-related; that is, as the number of tablets was increased, the number of attacks decreased.

Although the mechanism of action of colchicine in Familial Mediterranean Fever is unknown, Dr. Wolff and his co-workers raise a word of caution regarding its prolonged use. Colchicine is known to affect cell division and thus to have a potential for altering chromosomes. This is important because many FMF patients are young (attacks usually begin before age 15) and in their reproductive period.

Dr. Wolff and Charles A. Dinarello, M.D., David C. Dale, M.D., and David W. Alling, M.D., of NIAID; and Stephen E. Goldfinger, M.D. of the Massachusetts General Hospital, presented their findings at the annual meeting of the American Association of Physicians, May 7, 1974. Dr. Wolff is chief of NIAID's Laboratory of Clinical Investigations.

Research Advances

NEW SELENOPROTEIN MAY AID
IN MUSCULAR DYSTROPHY RESEARCH

The element selenium was first discovered in 1817 and the first organic compound containing selenium was prepared in 1847. Eventually, in the 1930's, selenium was identified as a potent toxic substance for cattle and other livestock. However, only in the past 15 years has selenium been found to be an essential nutrient, in very small quantities, for animals and bacteria.

Evidence presented in 1957 indicated that selenium deficiency caused rats to develop severe liver damage. At the same time, a research group reported that selenium prevented a fatal blood disease known as exudative diathesis in young chickens. In the next three to four years, white muscle disease, a form of muscular dystrophy in cattle and sheep, also became widely recognized as a selenium-deficiency disease. In 1973, scientific teams showed that selenium is an essential part of the enzyme glutathione peroxidase. This enzyme, which protects red blood cells against harmful oxidizing agents (peroxides) and radiation damage, is found in the red blood cells of cattle, sheep, rats, poultry and, presumably, man.

Recently, a new selenoprotein, a complex of protein with selenium, was isolated from a bacterium called *Clostridium sticklandii* that grows only in an oxygen-free atmosphere. This *Clostridium* was discovered several years ago by Thressa C. Stadtman, Ph.D. of the Laboratory of Biochemistry, National Heart and Lung Institute. From it, Dr. Stadtman has now isolated the new biochemical entity that contains selenium. She reports that it is essential for one of the chemical reactions which allows the bacterium to obtain energy for growth and

(more)

Selenoprotein (Cont'd)

to produce the energy-rich compound, adenosinetriphosphate, or ATP. (ATP is a substance that is critical for many chemical reactions in all living things.)

The new bacterial selenoprotein is similar in size to a selenoprotein reported in 1973 in the muscles of healthy lambs. When the muscle selenoprotein is missing, the growing lambs develop a form of muscular dystrophy. It is believed that this small muscle protein may be critical in supplying energy for the normal growth of the heart and skeletal muscles of the young animals. Thus, the bacterial and the muscle selenoproteins may have a similar function in reactions essential to growth.

Since the bacterial selenoprotein is easy to obtain in pure form and in quantities necessary for detailed study, it may also prove to be useful in research on certain types of muscular dystrophy.

Dr. Stadtman described her discovery of the new bacterial selenoprotein in *Science*, March 8, 1974.

#

LOW BIRTH WEIGHT--In the United States, low birth weight is the most important single factor linked to the high infant mortality rate, according to the National Institutes of Health.

Research Advances

NEW TEST DIAGNOSES
KIDNEY INFECTIONS

The presence of antibody-coated bacteria in urine is a reliable indicator of kidney infection. This finding may enable physicians to spot such involvement earlier and treat it more adequately.

It is often impossible to distinguish between kidney (upper) and lower urinary tract infection on the basis of clinical signs and history alone. Direct methods of pinpointing the site of infection, however, are difficult and hazardous, while indirect tests have, until now, proved unreliable.

Recently, investigators at the University of Texas Medical School at San Antonio described a simple technique for detecting antibody-coated bacteria in urine sediment that appeared to indicate whether or not there was kidney involvement. In the present study, a group of researchers at the University of Texas Southwestern Medical School, the Veterans Administration Hospital, and Parkland Memorial Hospital in Dallas, Texas, compared results from this new test with findings from bladder-washout--a direct method for localizing urinary tract infections.

The researchers studied 29 adults, all of whom had bacteria in their urine and many of whom had additional signs of upper or lower urinary tract infection. According to the results of bladder-washout, infection was confined to the lower urinary tract in eight of the patients. None of these patients had antibody-coated bacteria in their urine. In contrast, 17 of 18 patients with upper tract involvement, as diagnosed by bladder-washout, did have coated bacteria. Clearly, in these 26 patients the new test furnished a reliable indication of whether or not the upper urinary tract was infected.

(more)

Kidney (Cont'd)

In the three remaining patients, bladder-washout gave equivocal results. However, urine specimens from these patients contained coated bacteria, suggesting that they may indeed have had upper tract involvement.

Availability of this rapid, simple, risk-free technique could significantly affect understanding and management of urinary tract illnesses. Widespread use of the test would provide a clearer picture of the course and outcome of kidney as opposed to bladder infection. Also, the new technique can be performed in the hospital laboratory, and results can be made available early in the course of the disease and used to help plan rational therapy for the individual patient.

Stephen R. Jones, M.D., James W. Smith, M.D., and Jay P. Sanford, M.D., reported their findings in the March 14 issue of *The New England Journal of Medicine*. The original description of the test for antibody-coated bacteria in urine sediment appears in the same issue. Their work was supported by the National Institute of Allergy and Infectious Diseases.

#

CONGENITAL MALFORMATIONS--In the United States in a single year, as many as 200,000 children will be born with one or more congenital anomalies. These malformations probably result from an interaction between genetic and environmental causes, according to the National Institutes of Health.

Photo Feature

Parents With Parents...

CLEFT PALATE GROUP
COUNSELS MOTHERS

A group of mothers of cleft palate children are helping themselves adjust to their children's conditions--and they are helping other mothers at the same time.

The Cleft Palate Center of the University of Pittsburgh began a group therapy program for mothers of cleft palate children in 1970. Eight mothers whose children were receiving treatment at the Center took part in eleven weekly sessions with two group therapists. The mothers became so actively-involved in the group that, by the end of the sessions, they were able to work out guilt feelings surrounding the birth of the child with a defect and to cope with the problems of caring for the child.

Because the mothers were so unwilling to end this experience, the Center staff set up a six-month program to train the women as paraprofessional group leaders for therapy sessions with other mothers. Five of the original group were available to participate in the training. As a result, three new groups were formed with two trained mothers working together as co-leaders in each new group.

At the end of the first year, the women were leading a total of five eight-week programs. In spite of some difficulties involved with the project, the mothers were enthusiastic about carrying on their success.

As a direct outgrowth of these efforts, the mothers and other parents have become involved in a variety of activities, including a mother's hospital visitation project; a parents' association which is actively involved in

(more)

Cleft Palate (Cont'd)

raising funds for the Center; a series of "Information Day" meetings where speakers explain the care, handling, and specific problems of cleft children; an expressive art group for adolescents with clefts; and a creative drama children's group for younger cleft patients.

The hospital visitation program resulted from the realization that at the time a child is born with a cleft, the mother may wish desperately to talk with another mother of a cleft child. The Center staff had considered starting a program in which the mothers' group would make hospital visits, but were uncertain whether the mothers were adequately trained.

While the pros and cons of the arrangement were being debated, a worried physician called the Center when he was faced with a couple who did not want
(more)



Mrs. Audrey Verdu (center), a Group Leader and Volunteer in the Parents with Parents program at the Cleft Palate Center, meets with mothers of cleft palate patients. (NIH Photo #1263)

Cleft Palate (Cont'd)

to take their cleft child home. One of the group-trained mothers went to the hospital, answered questions for the couple, and helped them adjust to the situation. Now, the child and parents are together and doing well and, as a result, a hospital visitation program is under way.

As another important outgrowth of this innovative program, the original mothers have realized their leadership potential and are changing their life styles and pursuing interests of their own apart from their families.

One mother is about to begin nursing training and two have started to take courses in college. Another mother works full-time at the Center as a secretary and is rapidly becoming an expert on feeding techniques for cleft children. This woman has also entered the University of Pittsburgh where, by special examination, she placed three credits hours short of junior standing.

Betty Jane McWilliams, Ph.D., and Eleanor C. Irwin, Ph.D., of the University of Pittsburgh described the Cleft Palate Program in *Cleft Palate Journal*, October 1973. The work was supported in part by a grant from the National Institute of Dental Research.

#

DEFECTIVE LEARNING CAPACITIES--The human infant and child may exhibit a defective learning capacity if subjected to an inadequate diet, according to the National Institutes of Health.

Photo Feature

THE "BODY BOX" INCREASES
PULMONARY DISEASE DETECTION

A pulmonary function testing device, known as the "Body Box", is being used at the Loma Linda University Medical Center. With it, the possibility of detecting pulmonary disease is increased. The box's system interacts with the Loma Linda Scientific Computation Facility which is supported by the Division of Research Resources. The patient's lung capacity and rates of air intake and output are recorded directly to the graphics display terminal, converted to flow-volume curves for comparison of normal and abnormal curves, and finally displayed on the graphics terminal as a spirogram. It is through the spirometry series that the existence of possible pulmonary disease can be quickly recognized. The door is closed on the "Body Box" when in actual use. (NIH Photo #1264)

News Feature

SCREENING TESTS IDENTIFY
CYSTIC FIBROSIS CARRIERS

Cystic fibrosis, an inherited metabolic disease, is transmitted to a child only when both parents are carriers of the trait.

Although effective screening tests have been developed for other genetic disorders, such as Tay-Sachs disease and sickle cell anemia, a simple and reliable method of detecting carriers of the cystic fibrosis trait has eluded investigators. Recently, however, researchers have developed new tests to identify carriers of cystic fibrosis.

Barbara Bowman, Ph.D., at the University of Texas, Galveston, has isolated and identified a substance in the blood of both cystic fibrosis patients and carriers which inhibits ciliary action. Although the presence of this factor was noted in 1967, investigators had been unable to isolate it from the blood serum until now.

Previous research had demonstrated that serum or serum fractions from cystic fibrosis patients and carriers inhibited ciliary action in rabbit trachea and in fresh water clams. Dr. Bowman has now tested the newly-isolated material on the cilia in oyster gills with the same result. A similar test with blood serum using rabbit cilia has been developed by Kurt Hirschhorn, M.D., and associates at the Mount Sinai Medical School, New York.

The significance of the development of tests to identify carriers lies in their application for genetic counseling. When only one parent carries the cystic fibrosis trait, the children will not inherit the disease (although some could be carriers). If both parents are carriers, however, there is a one-in-four chance of cystic fibrosis occurring in their children. Since

(more)

Cystic Fibrosis (Cont'd)

carriers exhibit no clinical symptoms of the disorder, a reliable and simple method of pinpointing them would be invaluable.

An estimated one baby in every 1,400 is born with cystic fibrosis, which is characterized by malfunctioning exocrine glands, causing several clinical problems. Loss of large amounts of salt through the sweat can become a very serious problem in hot weather, causing dehydration or heat exhaustion.

The mucus-secreting glands of a cystic fibrosis patient produce abnormally thick, viscous mucus which tends to obstruct the ducts or openings of the glands. When the mucus accumulates in the ducts of the pancreas, it interferes with the ability of this gland to supply digestive enzymes to the intestinal tract, thus leading to poor digestion and malabsorption of a number of nutrients.

The most serious complication of cystic fibrosis is the development of progressive, chronic lung disease. Thick mucus obstructs the smaller air passages in the lung, causing labored breathing and a chronic cough. In time, bacteria multiply in the accumulated secretions, predisposing the child to chronic bronchitis or pneumonia--a leading cause of death in these patients. The lung changes also may restrict pulmonary blood flow, leading to increased blood pressure in the lung and to consequent chronic heart strain and eventual heart failure.

Cystic fibrosis research is now focused on a wide range of problems, including the improvement of antibiotic therapy to retard the progression of chronic pulmonary disease, the most frequent fatal complication of cystic fibrosis; refinement of precise screening techniques to identify carriers of the cystic fibrosis trait; and identification of the underlying metabolic defect in the disorder.



Photo Feature

EELS AND COBRA VENOM CONTRIBUTE
TO MYASTHENIA GRAVIS RESEARCH

Scientists at the Salk Institute believe they have produced an experimental model of myasthenia gravis, a fatal degeneration of neuromuscular communication in man. This discovery came as a result of their research to isolate the receptor for acetylcholine, the chemical released by nerves to transmit their signals to muscles.

Jim Patrick, Ph.D., and Jon Lindstrom, Ph.D., of La Jolla, California, used cobra venom in their research to isolate the acetylcholine receptor from the electric organs of eels. When the scientists poured a mixture of eel membrane extract through radioactive cobra toxin, the toxin adsorbed the receptor from the solution to separate it from contaminants.

The researchers then injected the highly purified receptor into rabbits. The rabbits not only developed antibodies which blocked the activity of eel electric cells, but also developed antibodies which blocked the rabbits' own muscle activity. In effect, the experiment produced an autoimmune reaction in the animals.



*Dr. Jon Lindstrom and electric eel.
(NIH Photo #1265)*

The rabbits developed a form of paralysis which seems to mimic myasthenia gravis in humans, offering researchers an animal model of this fatal disease.

Dr. Patrick is a grantee of the National Institute of Neurological Diseases and Stroke.

Medical News Tip

INFECTION AND TRAUMA--The successful treatment of trauma patients is still one of the greatest challenges facing surgery today. And infection, one of its major unsolved complications, continues to add to its seriousness as a health hazard. Sepsis in the trauma patients is a very significant and complex phenomenon which continually changes.

The application of germ concepts, antiseptic and aseptic techniques, immunization procedures, and the general use of antibiotics for a third of a century have had revolutionary effects on the control of infection. However, statistics from 1967 show that about 3 1/2 million infections occurred in hospitalized patients, at an estimated cost of \$9.8 billion in this country.

For additional information about National Institute of General Medical Sciences programs of control of infection after trauma, contact:

NIGMS
Bldg. 31, Room 4A-46
Bethesda, MD 20014
Phone: (301) 496-5676

#



New Publication:Dust Allergy

House dust is perhaps the most common cause of dust allergy. This "occupational" plague of the housewife is often the source of troublesome allergy symptoms such as watery, itching eyes or a runny, sneezy nose.

A new publication, *Dust Allergy*, prepared by the National Institute of Allergy and Infectious Diseases, explains the possible causes and treatments available for house dust allergy.

An allergy is an abnormal sensitivity to a substance called an allergen. The allergen has not been identified in house dust, because the dust is composed of many potential allergenic materials such as cotton linters, stuffing material from pillows or mattresses, and food particles.

A major area of current research on this problem is the relation of mites to the allergenicity of house dust. This small spider-like insect is found in worldwide house dust samplings. Researchers are now trying to determine whether the hard, outer shell of the mite itself is allergenic or whether these creatures secrete or excrete an allergenic substance.

There is no cure for dust allergy; however, there are several methods of testing and treatment available, including skin tests, medications, and allergy shots. An extensive anti-dust program in the home is of primary importance in treating house dust allergy.

Science writers can obtain a free copy of this publication from:

NIAID
National Institutes of Health
Building 31, Room 7A-32
Bethesda, MD 20014
Phone: (301) 496-5717

News Releases Issued

CANCER CENTERS--The National Cancer Institute has established four additional Comprehensive Cancer Center Programs to conduct research and bring results rapidly to a maximum number of people. The new programs include: the Yale University Medical School Program; the Georgetown University-Howard University Program; the Illinois Cancer Council Program, Chicago; the Colorado Regional Cancer Center, Denver. Nine other Center Programs were established in 1973 and three existed before passage of the National Cancer Act in 1971.

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